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L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis (Review)

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[Intervention Review]

L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis

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ABSTRACT

Background

Hepatic encephalopathy is a common complication of cirrhosis and has high associated morbidity and mortality. The condition is classified as *overt* if it is clinically apparent or *minimal* if only evident though psychometric testing. The exact pathogenesis of this syndrome is unknown although ammonia is thought to play a key role. L-ornithine L-aspartate has ammonia-lowering properties and may, therefore, benefit people with cirrhosis and hepatic encephalopathy.

Objectives

To evaluate the beneficial and harmful effects of L-ornithine L-aspartate versus placebo, no intervention, or other active interventions in people with cirrhosis and hepatic encephalopathy.

Search methods

We undertook electronic searches of The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, LILACS and Science Citation Index Expanded to December 2017 and manual searches of meetings and conference proceedings; checks of bibliographies; and corresponded with investigators and pharmaceutical companies.

Selection criteria

We included randomised clinical trials, irrespective of publication status, language, or blinding. We included participants with cirrhosis who had minimal or overt hepatic encephalopathy or who were at risk for developing hepatic encephalopathy. We compared: L-ornithine L-aspartate versus placebo or no intervention; and L-ornithine L-aspartate versus other active agents such as non-absorbable disaccharides, antibiotics, probiotics, or branched-chain amino acids.

Data collection and analysis

Two review authors, working independently, retrieved data from published reports and correspondence with investigators and pharmaceutical companies. The primary outcomes were mortality, hepatic encephalopathy, and serious adverse events. We undertook meta-analyses and presented the results as risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI). We assessed bias control using the Cochrane Hepato-Biliary Group domains; we evaluated the risk of publication bias and other small trial effects in

regression analyses; conducted subgroup and sensitivity analyses; and performed Trial Sequential Analyses. We determined the quality of the evidence using GRADE.

Main results

We identified 36 randomised clinical trials, involving at least 2377 registered participants, which fulfilled our inclusion criteria including 10 unpublished randomised clinical trials. However, we were only able to access outcome data from 29 trials involving 1891 participants. Five of the included trials assessed prevention, while 31 trials assessed treatment. Five trials were at low risk of bias in the overall assessment of mortality; one trial was at low risk of bias in the assessment of the remaining outcomes.

L-ornithine L-aspartate had a beneficial effect on mortality compared with placebo or no intervention when including all trials (RR 0.42, 95% CI 0.24 to 0.72; I^2 = 0%; 19 trials; 1489 participants; very low quality evidence), but not when the analysis was restricted to the trials at low risk of bias (RR 0.47, 95% CI 0.06 to 3.58; 4 trials; 244 participants). It had a beneficial effect on hepatic encephalopathy compared with placebo or no intervention when including all trials (RR 0.70, 95% CI 0.59 to 0.83; 22 trials; 1375 participants; I^2 = 62%; very low quality evidence), but not in the one trial at low risk of bias (RR 0.96, 95% CI 0.85 to 1.07; 63 participants). The analysis of serious adverse events showed a potential benefit of L-ornithine L-aspartate when including all randomised clinical trials (RR 0.63, 95% CI 0.45 to 0.90; 1 trial; 1489 participants; I^2 = 0%; very low quality evidence), but not in the one trial at low risk of bias for this outcome (RR 0.83, 95% CI 0.15 to 4.65; 63 participants). The Trial Sequential Analyses of mortality, hepatic encephalopathy, and serious adverse events found insufficient evidence to support or refute beneficial effects. Subgroup analyses showed no difference in outcomes in the trials evaluating evaluating the prevention or treatment of either overt or minimal hepatic encephalopathy or trials evaluating oral versus intravenous administration We were unable to undertake a meta-analysis of the three trials involving 288 participants evaluating health-related quality of life. Overall, we found no difference between L-ornithine L-aspartate and placebo or no intervention in non-serious adverse events (RR 1.15, 95% CI 0.75 to 1.77; 14 trials; 1076 participants; I^2 = 40%). In comparison with lactulose, L-ornithine L-aspartate had no effect on mortality (RR 0.68, 95% CI 0.11 to 4.17; 4 trials; 175 participants; I^2 = 0%); hepatic encephalopathy (RR 1.13, 95% CI 0.81 to 1.57); serious adverse events (RR 0.69, 95% CI 0.22 to 2.11); or non-serious adverse events (RR 0.05, 95% CI 0.01 to 0.18). In comparison with probiotics, L-ornithine L-aspartate had no effect on mortality (RR 1.01, 95% CI 0.11 to 9.51); serious adverse events (RR 1.07, 95% CI 0.23 to 4.88); or changes in blood ammonia concentrations from baseline (RR -2.30 95% CI -6.08 to 1.48), but it had a possible beneficial effect on hepatic encephalopathy (RR 0.71, 95% CI 0.56 to 0.90). Finally, in comparison with rifaximin, L-ornithine L-aspartate had no effect on mortality (RR 0.33, 95% CI 0.04 to 3.03; 2 trials; 105 participants); hepatic encephalopathy (RR 1.06, 95% CI 0.57 to 1.96); serious adverse events (RR 0.32, 95% CI 0.01 to 7.42), or non-serious adverse events (RR 0.32, 95% CI 0.01 to 7.42).

Authors' conclusions

The results of this review suggest a possible beneficial effect of L-ornithine L-aspartate on mortality, hepatic encephalopathy, and serious adverse events in comparisons with placebo or no-intervention, but, because the quality of the evidence is very low, we are very uncertain about these findings. There was very low quality evidence of a possible beneficial effect of L-ornithine L-aspartate on hepatic encephalopathy, when compared with probiotics, but no other benefits were demonstrated in comparison with other active agents. Additional access to data from completed, but unpublished trials, and new randomised placebo-controlled, double-blind clinical trials are needed.

PLAIN LANGUAGE SUMMARY

L-ornithine L-aspartate for people with chronic liver disease and hepatic encephalopathy (poor brain functioning)

Background

Cirrhosis is a chronic disorder of the liver. People with this condition commonly develop hepatic encephalopathy, a complication that results in poor brain functioning. Some people with cirrhosis develop obvious clinical features of disturbed brain functioning, such as difficulties with speech, balance and daily functioning; they are said to have *overt* hepatic encephalopathy; the changes may be short-lived, may recur, or may persist for long periods. Other people with cirrhosis may show no obvious clinical changes but some aspects of their brain function, such as attention and the ability to perform complex tasks are found to be impaired when tested; they are said to have minimal hepatic encephalopathy. The reason why people develop hepatic encephalopathy is complex, but the accumulation in the blood of toxins from the gut, particularly of a compound called ammonia, plays a key role. L-ornithine L-aspartate lowers blood ammonia levels and so may have beneficial effects in people with hepatic encephalopathy or help stop them developing it.

Review question

We investigated the use of L-ornithine L-aspartate given either by mouth (oral) or into a vein in an fluid drip (intravenous) for the prevention and treatment of hepatic encephalopathy by reviewing clinical trials in which people with cirrhosis were randomly allocated to treatment with L-ornithine L-aspartate, to an inactive dummy (called placebo), to no treatment, or to another medicine for this condition such as lactulose, probiotics and rifaximin. We included participants with cirrhosis who had overt or minimal hepatic encephalopathy or who were at risk for developing this complication.

Search date

December 2017.

Study funding sources

Six of the 36 randomised clinical trials we included received no funding or any other support from pharmaceutical companies. Seventeen trials received financial support from pharmaceutical companies and a further three received L-ornithine L-aspartate or inactive placebo free of charge; there was no information on funding in the remaining 10 trials.

Study characteristics

We included 33 randomised clinical trials comparing L-ornithine L-aspartate with inactive placebo or no intervention and six randomised clinical trials comparing L-ornithine L-aspartate with other anti-encephalopathy treatments; some trials included more than one comparison. Five of the included trials tested L-ornithine L-aspartate for the prevention of hepatic encephalopathy while 30 trials tested its use as treatment for people with acute, chronic, or minimal hepatic encephalopathy. The length of treatment varied from three to 35 days in the trials testing the intravenous preparation (average eight days) and from seven to 180 days in those testing the oral preparation (average 30 days).

Key results

Our analyses showed L-ornithine L-aspartate might reduce deaths, improve hepatic encephalopathy, and prevent serious side effects compared with placebo or no treatment, but that it had no additional beneficial effects when compared with other medicines used to prevent and treat this condition.

Quality of the evidence

The evidence we found was very weak, and so we are not confident that L-ornithine L-aspartate is of use for preventing or treating hepatic encephalopathy in people with cirrhosis. Many studies were unpublished and so had not been carefully vetted, and many of the published trials received support from the pharmaceutical industry which introduces an element of bias. Accordingly, more information is needed before the value of L-ornithine L-aspartate for preventing and treating hepatic encephalopathy can be determined.

Summary of findings for the main comparison. L-ornithine L aspartate compared to placebo or no intervention for people with cirrhosis and hepatic encephalopathy

L-ornithine L aspartate compared to placebo or no intervention for people with cirrhosis and hepatic encephalopathy or at risk of developing hepatic encephalopathy

Participants: people with cirrhosis who had minimal or overt hepatic encephalopathy or who were at risk for developing hepatic encephalopathy; regardless of sex, age, aetiology, and severity of the underlying liver disease, or the presence of identified precipitating factors

Setting: hospital or outpatient

Intervention: L-ornithine L-aspartate

Comparison: placebo or no intervention

Outcomes: all outcomes assessed at maximum duration of follow-up

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with L-ornithine L aspartate				
Mortality	**Study population**		**RR 0.42** (0.24 to 0.72)	1489 (19 RCTs)	⊕⊖⊖⊖ **Very low**[1]	-
	57 per 1000	**24 per 1000** (14 to 41)				
Hepatic encephalopathy assessed based on neurocognitive manifestations	**Study population**		**RR 0.70** (0.59 to 0.83)	1375 (22 RCTs)	⊕⊖⊖⊖ **Very low**[2]	-
	470 per 1000	**329 per 1000** (277 to 390)				
Serious adverse events assessed using ICH-GCP	**Study population**		**RR 0.63** (0.45 to 0.90)	1489 (19 RCTs)	⊕⊖⊖⊖ **Very low**[3]	-
	100 per 1000	**63 per 1000** (45 to 90)				
Quality of life assessed using 3 different questionnaires	3 RCTs evaluated health-related quality of life in participants with minimal hepatic encephalopathy. 1 found no difference between interventions based on the Liver Disease Quality of Life Assess-		(See comment)	-	⊕⊖⊖⊖ **Very low**[4]	-

	ment. 2 found a beneficial effect based on the total Sickness Impact Profile score.					
Non-serious adverse events assessed using ICH-GCP	**Study population**		**RR 1.15** (0.75 to 1.77)	1076 (14 RCTs)	⊕⊖⊖⊖ **Very low**[5]	Reported non-serious adverse events included gastrointestinal discomfort (e.g. change in bowel habits and bloating), headache, pruritus, and fatigue
	128 per 1000	**147 per 1000** (96 to 226)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CHBG: Cochrane Hepato-Biliary Group; **CI:** confidence interval; **GCP:** Good Clinical Practice; **ICH:** International Conference on Harmonisation; **RCT:** randomised clinical trial; **RR:** risk ratio; **TSA:** Trial Sequential Analysis.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded 3 levels due risk of bias (result not confirmed in analyses of trials with a low risk of bias assessed using CHBG domains); evidence of publication bias (we were unable to gather data from unpublished trials); and imprecision (the TSA ignored the monitoring boundary).
[2]Downgraded 3 levels due risk of bias (result not confirmed in analyses of trials at low risk of bias assessed using CHBG domains; only 1 trial had a low risk of bias); evidence of publication bias (we were unable to gather data from unpublished trials); and inconsistency (I^2 value of 63% and visual inspection of the forest plots suggested a risk of inconsistency).
[3]Downgraded 3 levels due risk of bias (result not confirmed in analyses of trials at low risk of bias assessed using CHBG domains; only 1 trial had a low risk of bias); evidence of publication bias (we were unable to gather data from unpublished trials); and imprecision (the TSA ignored the monitoring boundary).
[4]Downgraded 3 levels due to risk of bias (result not confirmed in analyses of trials at low risk of bias assessed using CHBG domains; none of the trials had a low risk of bias); evidence of publication bias (we were unable to gather data from unpublished trials); imprecision (we were only able to evaluate trials individually; trials reporting this outcome were small with wide CIs).
[5]Downgraded 3 levels due to risk of bias (result not confirmed in analyses of trials at low risk of bias assessed using CHBG domains; only 1 trial had a low risk of bias); evidence of publication bias (we were unable to gather data from unpublished trials); imprecision (trials reporting this outcome were small and the meta-analysis result had wide CIs).

Summary of findings 2. L-ornithine L-aspartate compared to lactulose for people with cirrhosis and hepatic encephalopathy

L-ornithine L-aspartate compared to lactulose for people with cirrhosis and hepatic encephalopathy

Patient or population: people with cirrhosis who had minimal or overt hepatic encephalopathy or who were at risk for developing hepatic encephalopathy; regardless of sex, age, aetiology, and severity of the underlying liver disease or the presence of identified precipitating factors

Setting: hospital or outpatient

Intervention: L-ornithine L-aspartate

Comparison: lactulose

Outcomes: all outcomes assessed at maximum duration of follow-up

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with lactulose	Risk with L-ornithine L-aspartate				
Mortality	**Study population**		**RR 0.68** (0.11 to 4.17)	175 (4 RCTs)	⊕⊖⊖⊖ **Very low**[1]	-
	23 per 1000	**15 per 1000** (3 to 95)				
Hepatic encephalopathy assessed based on neurocognitive manifestations	Study population		**RR 1.13** (0.81 to 1.57)	175 (4 RCTs)	⊕⊖⊖⊖ **Very low**[2]	-
	364 per 1000	**411 per 1000** (295 to 571)				
Serious adverse events assessed using ICH-GCP	**Study population**		**RR 0.69** (0.22 to 2.11)	144 (3 RCTs)	⊕⊖⊖⊖ **Very low**[2]	-
	97 per 1000	**67 per 1000** (21 to 205)				
Quality of life assessed using questionnaires	No evidence was available for this outcome.					
Non-serious adverse events assessed using ICH-GCP	**Study population**		**RR 0.05** (0.01 to 0.18)	292 (2 RCTs)	⊕⊖⊖⊖ **Very low**[2]	-
	175 per 1000	**12 per 1000** (0 to 198)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CHBG: Cochrane Hepato-Biliary Group; **CI:** confidence interval; **GCP:** Good Clinical Practice; **ICH:** International Conference on Harmonisation; **RCT:** randomised clinical trial; **RR:** risk ratio; **TSA:** Trial Sequential Analysis.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded 3 levels due risk of bias (2 trials had a low risk of bias assessed using CHBG domains) and imprecision (wide CIs; small number of events/participants). We were unable to identify publication bias due to the small number of trials.
[2]Downgraded 3 levels due risk of bias (none of the included trials had a low risk of bias assessed using CHBG domains) and imprecision (wide CIs; small number of events/participants). We were unable to identify publication bias due to the small number of trials.

Summary of findings 3. L-ornithine L-aspartate compared to probiotic for people with cirrhosis and hepatic encephalopathy

L-ornithine L-aspartate compared to probiotic for people with cirrhosis and hepatic encephalopathy

Patient or population: people with cirrhosis who had minimal or overt hepatic encephalopathy or who were at risk for developing hepatic encephalopathy; regardless of sex, age, aetiology, and severity of the underlying liver disease, or the presence of identified precipitating factors

Setting: hospital or outpatient

Intervention: L-ornithine L-aspartate

Comparison: probiotic

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with probiotic	Risk with L-ornithine L-aspartate				
Mortality	**Study population**		**RR** 1.01 (0.11 to 9.51)	143 (2 RCTs)	⊕⊖⊖⊖ **Very low**[1]	-
	14 per 1000	**14 per 1000** (2 to 132)				
Hepatic encephalopathy assessed based on neurocognitive manifestations	Study population		**RR** 0.71 (0.56 to 0.90)	143 (2 RCTs)	⊕⊖⊖⊖ **Very low**[1]	-
	722 per 1000	**513 per 1000** (404 to 650)				

Serious adverse events assessed using ICH-GCP	**Study population**		**RR** 1.07 (0.23 to 4.88)	143 (2 RCTs)	⊕⊖⊖⊖ **Very low**[1]	-
	42 per 1000	**45 per 1000** (10 to 203)				
Quality of life assessed using questionnaires	No evidence available for this outcome.					
Non-serious adverse events assessed using ICH-GCP	No evidence available for this outcome.					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CHBG: Cochrane Hepato-Biliary Group; **CI:** confidence interval; **GCP:** Good Clinical Practice; **ICH:** International Conference on Harmonisation; **RCT:** randomised clinical trial; **RR:** risk ratio; **TSA:** Trial Sequential Analysis.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded 3 levels due risk of bias (the analysis only includes 1 trial with a high risk of bias assessed using CHBG domains) and imprecision (wide CIs). We were unable to identify publication bias and did not evaluate heterogeneity because the analysis only includes 1 trial.

Summary of findings 4. L-ornithine L-aspartate compared to rifaximin for people with cirrhosis and hepatic encephalopathy

L-ornithine L-aspartate compared to rifaximin for people with cirrhosis and hepatic encephalopathy

Patient or population: people with cirrhosis who had minimal or overt hepatic encephalopathy or who were at risk for developing hepatic encephalopathy; regardless of sex, age, aetiology, and severity of the underlying liver disease, or the presence of identified precipitating factors

Setting: hospital or outpatient

Intervention: L-ornithine L-aspartate

Comparison: rifaximin

Outcomes: all outcomes assessed at maximum duration of follow-up

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with rifaximin	Risk with L-ornithine L-aspartate				
Mortality	**Study population**		**RR 0.33** (0.04 to 3.03)	105 (2 RCTs)	⊕⊖⊖⊖ **Very low**[1]	-
	38 per 1000	**13 per 1000** (2 to 117)				
Hepatic encephalopathy assessed based on neurocognitive manifestations	**Study population**		**RR 1.06** (0.57 to 1.96)	105 (2 RCTs)	⊕⊖⊖⊖ **Very low**[2]	-
	269 per 1000	**285 per 1000** (153 to 528)				
Serious adverse events assessed using ICH-GCP	**Study population**		**RR 0.32** (0.01 to 7.42)	43 (1 RCT)	⊕⊖⊖⊖ **Very low**[2]	-
	48 per 1000	**15 per 1000** (0 to 353)				
Quality of life assessed using questionnaires	No evidence was available for this outcome.					
Non-serious adverse events assessed using ICH-GCP	**Study population**		**RR 0.32** (0.01 to 7.42)	43 (1 RCT)	⊕⊖⊖⊖ **Very low**[2]	-
	48 per 1000	**15 per 1000** (0 to 353)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CHBG: Cochrane Hepato-Biliary Group; **CI:** confidence interval; **GCP:** Good Clinical Practice; **ICH:** International Conference on Harmonisation; **RCT:** randomised clinical trial; **RR:** risk ratio; **TSA:** Trial Sequential Analysis.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded 3 levels due risk of bias (1 of the included trials had a low risk of bias assessed using CHBG domains) and imprecision (wide CIs; small number of events/participants). We were unable to identify publication bias due to the small number of trials.

2Downgraded 3 levels due risk of bias (the included trial had a high risk of bias assessed using CHBG domains) and imprecision (wide CIs; small number of events/participants). We were unable to identify publication bias due to the small number of trials.

BACKGROUND

Description of the condition

The term hepatic encephalopathy is used to describe the spectrum of neuropsychiatric change that can arise in people with cirrhosis. The joint guideline from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) defines hepatic encephalopathy as: "brain dysfunction associated with liver insufficiency or portal systemic shunting" (EASL/AASLD 2014a; EASL/AASLD 2014b).

Clinically apparent or *overt* hepatic encephalopathy manifests as a neuropsychiatric syndrome encompassing a wide spectrum of mental and motor disorders (Weissenborn 1998; Ferenci 2002). It may develop over a period of hours or days, apparently spontaneously, or else, in 50% to 70% of instances, follow an identifiable precipitating event such as: gastrointestinal bleeding, infection, or dietary indiscretion. Episodes may recur. Between episodes, people may return to their baseline neuropsychiatric status or retain a degree of impairment (Bajaj 2010). Less frequently, people present with persistent neuropsychiatric abnormalities, which are always present to some degree, but which may fluctuate in severity. The changes in *mental state* range from subtle alterations in personality, intellectual capacity, and cognitive function to deep coma. The changes in *motor function* may include rigidity, disorders of speech production, tremor, delayed diadochocinetic movements, hyper- or hyporeflexia, choreoathetoid movements, Babinsky's sign, and transient focal symptoms (Victor 1965; Weissenborn 1998; Cadranel 2001). Asterixis, also known as*a* flapping tremor, is the best-known motor abnormality. People with overt hepatic encephalopathy also show other abnormalities such as impaired psychomotor performance (Schomerus 1998); neurophysiological function (Parsons-Smith 1957; Chu 1997); and alterations in cerebral neurochemical/neurotransmitter homeostasis (Taylor-Robinson 1994), blood flow and metabolism (O'Carroll 1991), and cerebral fluid homeostasis (Haussinger 2000). In general, the degree of impairment in these variables increases with the severity of the underlying liver disease (Bajaj 2009).

Minimal hepatic encephalopathy (in the older literature 'subclinical' or 'latent') is the term used to describe the neuropsychiatric status of people with cirrhosis without apparent clinical neurocognitive deficits but who show abnormalities in neuropsychometric or neurophysiological performance (Ferenci 2002; Guérit 2009; Atluri 2011).

There is no gold standard for the diagnosis of hepatic encephalopathy; however, there are several diagnostic tests that can be used alone or in combination (Montagnese 2004). A full neuropsychiatric history and examination is necessary to identify abnormalities suggestive of hepatic encephalopathy such as: changes in memory, concentration, cognition, and consciousness and, equally importantly, to confirm their absence (Montagnese 2004). The West Haven Criteria are commonly used to assess changes in mental status (Conn 1977), while the Glasgow Coma Score is used to assess the level of consciousness (Teasdale 1974). It is also important to consider and exclude other potential causes of neuropsychiatric abnormalities including concomitant neurological disorders and other metabolic encephalopathies such as those associated with diabetes, renal failure, and chronic pulmonary disease (EASL/AASLD 2014a; EASL/AASLD 2014b).

People with hepatic encephalopathy show impairment on a range of psychometric tests. People with minimal hepatic encephalopathy show deficits in attention, visuospatial abilities, fine motor skills, or memory (Montagnese 2004; Randolph 2009), while people with overt hepatic encephalopathy show additional changes in psychomotor speed, executive function, and concentration. Several paper and pencil psychometric tests are used in the evaluation of cognitive performance. These tests are either used individually or are grouped together into test batteries or systems. Of these, the Number Connection Tests A & B are the best known (Ferenci 2002). The Psychometric Hepatic Encephalopathy Score (PHES), which comprises of five paper and pencil tests covering the domains of attention, visual perception, and visuoconstructive abilities, is the most widely used psychometric test battery and has high diagnostic specificity (Schomerus 1998; Weissenborn 2001); the test scoring needs adjustment for several confounding variables, such as age and level of education; many countries have now developed appropriate normative databases. In countries where levels of illiteracy are high, the Figure Connection Tests A & B are often used either alone or as part of the PHES battery (Dhiman 1995).

People with hepatic encephalopathy may also show several neurophysiological abnormalities (Guérit 2009). The electroencephalogram, which primarily reflects cortical neuronal activity, may show progressive slowing of background activity and abnormal wave morphology. Recent advances in electroencephalogram analysis allow provision of better quantifiable and more informative data (Jackson 2016; Olesen 2016). The brain responses, or evoked potentials, to stimuli such as light and sounds may show abnormal slowing or wave forms (or both) (Chu 1997; Guérit 2009). Other potential diagnostic techniques, such as the Critical Flicker Fusion Frequency (Kircheis 2002), and the Inhibitory Control Test, still need further validation (Bajaj 2008). Blood ammonia concentrations are not routinely measured to diagnose hepatic encephalopathy (Lockwood 2004; Blanco Vela 2011a), but are often monitored in clinical trials.

Description of the intervention

L-ornithine L-aspartate is a stable salt of the amino acids ornithine and aspartic acid. It can be administered both orally and intravenously (Rose 1998; Blanco Vela 2011b).

How the intervention might work

The exact pathogenesis of hepatic encephalopathy is unknown, but ammonia is known to play a key role (Butterworth 2014). The main sources of ammonia in the body are nitrogenous products in the diet, bacterial metabolism of urea and proteins in the colon, and the deamination of glutamine in the small intestine. The ammonia produced in the gut is absorbed into the portal vein, and together with the ammonia derived from hepatic amino acid metabolism, it is taken up by periportal hepatocytes and metabolised to urea via the urea cycle. Some ammonia is taken up by perivenous hepatocytes where it is converted to glutamine via glutamine synthetase. These two systems, working in concert, tightly control blood ammonia concentrations in the hepatic veins. The kidney and muscle also play a role in ammonia homeostasis (Wright 2011). In skeletal muscle, ammonia is transformed into glutamine through the action of glutamine synthetase. In the kidneys, ammonia is generated from the deamination of glutamine.

In people with cirrhosis this system for detoxifying ammonia can fail, first: because of failure of hepatocyte function, and second: because the presence of portal systemic collateral vessels allows blood to bypass the liver. As a result, gut-derived ammonia is not effectively cleared from the blood by the liver; it consequently enters the systemic circulation and impinges on the brain where it has both direct and indirect effects on cerebral function.

L-ornithine L-aspartate promotes hepatic removal of ammonia by stimulating residual hepatic urea cycle activity and promoting glutamine synthesis, particularly in skeletal muscle (Rose 1999). The ornithine moiety stimulates the activity of carbamoyl phosphate synthetase within the liver, while the aspartate moiety stimulates the activity of arginase through nitrogen donation. It also enhances the activities of ornithine and aspartate transaminases in peripheral tissues to promote the production of glutamate, which predominantly occurs in muscle (Gebhardt 1997; Rose 1998; Blanco Vela 2011a). Thus, L-ornithine L-aspartate has ammonia-lowering activities that might benefit people with hepatic encephalopathy.

Why it is important to do this review

Hepatic encephalopathy is a common and debilitating complication of cirrhosis. Approximately 10% to 14% of people with cirrhosis have overt hepatic encephalopathy when they are first diagnosed with liver disease (Saunders 1981). In people with decompensated cirrhosis, the prevalence of overt hepatic encephalopathy at presentation is about 20% (D'Amico 1986; de Jongh 1992; Zipprich 2012). In people with cirrhosis who have no evidence of neuropsychiatric impairment the risk of developing an episode of overt hepatic encephalopathy, within five years of presentation, varies from 5% to 25% depending on the presence or absence of other risk factors; the cumulated incidence of overt hepatic encephalopathy is as high as 40% (Randolph 2009; Bajaj 2011a). The prevalence of minimal hepatic encephalopathy may be more than 50% in people with previous overt hepatic encephalopathy (Sharma 2010; Lauridsen 2011).

The presence of hepatic encephalopathy, whether minimal or overt, is associated with significant impairment in the performance of complex tasks, such as driving (Schomerus 1981; Bajaj 2009; Kircheis 2009), and a detrimental effect on quality of life (Groeneweg 1998), and safety (Roman 2011). In addition, the presence of overt hepatic encephalopathy pre-transplantation has a detrimental effect on neurocognitive function post-transplantation (Sotil 2009), and on survival (Bustamante 1999; D'Amico 2006; Stewart 2007; Jepsen 2010). The one-year survival rate in people who have hepatic encephalopathy at presentation is 36%, with a five-year survival rate of 15% (Jepsen 2010), while the survival probability after a first episode of hepatic encephalopathy is 42% at one year but only 23% at three years (Bustamante 1999). Overt hepatic encephalopathy also poses a substantial burden for the carers of affected people (Bajaj 2011b), and a significant financial burden on healthcare systems (Poodad 2007; Stepanova 2012).

Means to prevent and treat hepatic encephalopathy in people with cirrhosis are clearly needed; L-ornithine L-aspartate, given its ammonia-lowering properties, is a potential candidate. The advantage of L-ornithine L-aspartate should it prove efficacious and safe, is that it is available as an oral preparation and an intravenous infusion; as such it may benefit people with acute (episodic) hepatic encephalopathy, which is particularly difficult to treat. However, the randomised clinical trials undertaken to date have reached different conclusions as did the five meta-analyses undertaken between 2000 and 2013 (Delcker 2000a; Jiang 2009; Soarez 2009; Perez Hernandez 2011; Bai 2013). Further, the EASL/AASLD guidelines stated, in relation to L-ornithine L-aspartate that intravenous L-ornithine L-aspartate can be used as an alternative or additional agent to treat people non-responsive to conventional therapy but that oral supplementation with L-ornithine L-aspartate is ineffective (EASL/AASLD 2014a; EASL/AASLD 2014b). However, no evidence base was provided for this position statement.

Therefore, we have conducted a systematic review with meta-analyses of all available randomised clinical trials of L-ornithine L-aspartate for hepatic encephalopathy in people with cirrhosis, following recommendations for best practice.

OBJECTIVES

To assess the beneficial and harmful effects of L-ornithine L-aspartate versus placebo, no intervention, or other active interventions for people with cirrhosis and hepatic encephalopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials regardless of their publication status, language, or blinding in our primary analyses. If, during the selection of trials, we identified observational studies (i.e. quasi-randomised studies, cohort studies, or patient reports) that reported adverse events caused by or associated with the interventions in our review, we included these studies in the review of adverse events. We did not specifically search for observational studies for inclusion in this review, which is recognised as a limitation.

Types of participants

We included participants with cirrhosis who had minimal or overt hepatic encephalopathy or who were at risk for developing hepatic encephalopathy. We included participants in our primary analyses regardless of sex, age, aetiology and severity of the underlying liver disease, or presence of identified precipitating factors. We excluded data on people with hepatic encephalopathy associated with acute liver failure or people with non-cirrhotic portal hypertension.

Types of interventions

We compared: L-ornithine L-aspartate versus placebo or no intervention; and L-ornithine L-aspartate versus other active agents such as non-absorbable disaccharides, antibiotics, probiotics, or branched-chain amino acids. We included trials irrespective of the dose, treatment duration, or mode of administration of the L-ornithine L-aspartate. We allowed co interventions if they were administered equally to all comparison groups.

We did not plan to include analyses of glycerol phenylbutyrate, ornithine phenylacetate, or spherical carbon adsorbents (AST-120), as these will be evaluated in a separate review (Zacharias 2017).

Types of outcome measures

We assessed all outcomes at the maximum duration of follow-up (Gluud 2017).

Primary outcomes

- All-cause mortality.
- Hepatic encephalopathy. We assessed the outcome using the primary investigators' overall assessment of the number of participants who developed hepatic encephalopathy; and the number of participants without a clinically relevant improvement in hepatic encephalopathy.
- Serious adverse events: defined as any untoward medical occurrence that led to death; was life threatening; required hospitalisation or prolongation of hospitalisation; or resulted in persistent or significant disability (ICH-GCP 1997). We analysed serious adverse events as a composite outcome (Gluud 2017).

Secondary outcomes

- Non-serious adverse events (all adverse events that did not fulfil the criteria listed under serious adverse events).
- Health-related quality of life.

Exploratory outcomes

- Arterial or venous blood ammonia concentration.

Search methods for identification of studies

The last search update was undertaken in December 2017.

Electronic searches

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register (December 2017; Gluud 2017), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2017, Issue 11), MEDLINE Ovid (1946 to December 2017), Embase Ovid (1974 to December 2017), LILACS (1982 to December 2017; Bireme), Science Citation Index Expanded (1900 to December 2017; Web of Science), and Conference Proceedings Citation Index - Science (1990 to December 2017; Web of Science) (Royle 2003), using the strategies and time spans detailed in Appendix 1. We did not have access to Chinese or Japanese databases but plan to search these in future updates should they become available to us via the Cochrane Hepato-Biliary Group.

Searching other resources

We scanned the reference lists of relevant articles identified in the electronic searches, and proceedings from meetings of the British Society for Gastroenterology (BSG), the British Association for the Study of the Liver (BASL), the EASL, the United European Gastroenterology Week (UEGW), the American Gastroenterological Association (AGA), the AASLD, and the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN). We wrote to the principal authors of trials and the pharmaceutical companies involved in the manufacture and marketing of L-ornithine L-aspartate for additional information about both completed and ongoing trials.

We also searched online trial registries such as ClinicalTrial.gov (clinicaltrials.gov/); the European Medicines Agency (EMA) (www.ema.europa.eu/ema/); the World Health Organization International Clinical Trial Registry Platform (www.who.int/ictrp); and the Food and Drug Administration (FDA) (www.fda.gov), as well as pharmaceutical company sources for ongoing or unpublished trials and Google Scholar. We used the same or similar search terms to those used for searching the electronic databases (Appendix 1).

Data collection and analysis

Selection of studies

Three review authors (ETG, MYM, and CS), working independently, read the electronic search output, performed additional manual searches, and listed potentially eligible trials. One review author (MYM) liaised with the authors and pharmaceutical sponsor of identified unpublished trials to seek their release. All review authors read the potentially eligible trials and participated in the final selection of trials for inclusion. For trials described in more than one publication, we selected the paper with the longest duration of follow-up as our primary reference. We listed details of all the included studies in the Characteristics of included studies table, and listed all the excluded trials with the reasons for their exclusion in the Characteristics of excluded studies table. A fourth review author (LLG) acted as ombudsman in case of disagreements on trial suitability for inclusion or exclusion. We resolved contrary opinions through discussion.

Data extraction and management

All review authors participated in data extraction and at least two review authors independently evaluated each randomised clinical trial. We asked medical professionals fluent in the language of the publication to translate foreign language papers. We requested missing data and other information from the published trial reports through correspondence with the authors of the included trials. We sought information and data from identified but unpublished trials by correspondence with trial authors and sponsors.

We gathered the following data from the included trials:

- Trials: design (cross-over or parallel); settings (number of clinical sites; outpatient or inpatient; inclusion period); country of origin; inclusion period; publication status;
- participants: mean age, proportion of men, aetiology of cirrhosis, type of hepatic encephalopathy (diagnostic criteria and definitions/terminology), previous history of hepatic encephalopathy;
- interventions: type, dose, duration of therapy, mode of administration;
- primary and secondary outcome data, including the definitions used in the assessment of overall improvement of hepatic encephalopathy, and bias control.

Assessment of risk of bias in included studies

We assessed bias control using the domains described in the Cochrane Hepato-Biliary Group module (Gluud 2017), and classified the risk of bias for separate domains as high, unclear, or low (Higgins 2011). We also included an overall assessment of bias control for both mortality and non-mortality outcomes.

Allocation sequence generation

- Low risk of bias: sequence generation achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice were adequate only if performed by an independent person.

- Unclear risk of bias: not described.
- High risk of bias: sequence generation method was not random.

Allocation concealment

- Low risk of bias: allocation by a central and independent randomisation unit, administration of coded, identical drug containers/vials or sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: not described.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and personnel using placebo, double dummy, or similar. We defined lack of blinding as not likely to affect the assessment of mortality.
- Unclear risk of bias: not described.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding (non-mortality outcomes).

Blinding of outcome assessors

- Low risk of bias: blinding of the outcome assessor using a placebo, double dummy, or similar. We defined lack of blinding as not likely to affect the assessment of mortality.
- Unclear risk of bias: insufficient information.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding (non-mortality outcomes).

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The investigators used sufficient methods, such as intention-to-treat analyses with multiple imputations or carry-forward analyses, to handle missing data.
- Unclear risk of bias: insufficient information.
- High risk of bias: results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: trial reported clinically relevant outcomes such as mortality, hepatic encephalopathy, and serious adverse events. If we had access to the original trial protocol, the outcomes selected were those described in the protocol. If we obtained information from a trial registry (such as www.clinicaltrials.gov), we only used that information if the investigators registered the trial before inclusion of the first participant.
- Unclear risk of bias: not all predefined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined outcomes were not reported.

For-profit bias

- Low risk of bias: trial appeared free of industry sponsorship or other type of for-profit support.
- Unclear risk of bias: insufficient information about support or sponsorship.
- High risk of bias: trial received funding or other support from a pharmaceutical company including the provision of trial drugs.

Other bias

- Low risk of bias: trial appeared free of other biases including: medicinal dosing problems or follow-up (as defined below).
- Unclear risk of bias: trial may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could have put it at risk of bias such as the administration of inappropriate treatments being given to the controls (e.g. an inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups).

Overall bias assessment

- Low risk of bias: all domains were low risk of bias using the definitions described above.
- High risk of bias: one or more of the bias domains were of unclear or high risk of bias.

Measures of treatment effect

We used risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, both with 95% confidence intervals (CI). We also used Trial Sequential Analysis-adjusted CI.

Unit of analysis issues

We included randomised clinical trials using a parallel group design; we only included data from the first treatment period of cross-over trials (Higgins 2011). We included separate pair-wise comparisons from multi-arm trials. Accordingly, if a trial compared L-ornithine L-aspartate, rifaximin, and lactulose, we conducted separate analyses for L-ornithine L-aspartate versus rifaximin and L-ornithine L-aspartate versus lactulose.

Dealing with missing data

We extracted data on all randomised participants to allow intention-to-treat analyses. We planned to undertake analyses, using simple imputation, to evaluate the potential influence of missing outcome data (Higgins 2008), including 'worst-case' and 'best-case' scenario analyses in which participants in the intervention arm with missing outcome data would be classified as failures while their counterparts in the control arm would be classified as successes and vice versa (Gluud 2017).

Assessment of heterogeneity

We evaluated heterogeneity based on visual inspection of forest plots and expressed heterogeneity as I^2 values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and greater than 80% (considerable). We included the information in the 'Summary of findings' tables.

Assessment of reporting biases

For meta-analyses with at least 10 randomised clinical trials, we assessed reporting biases through regression analyses and visual inspection of funnel plots (Harbord 2006).

Data synthesis

We performed the analyses in Review Manager 5 (RevMan 2014), STATA (Stata 14), and Trial Sequential Analysis (TSA 2011).

Meta-analysis

In our primary analyses, we stratified randomised clinical trials based on the type of control intervention (i.e. placebo or no intervention, non-absorbable disaccharides, antibiotics, and probiotics). We compared the fixed-effect and random-effects estimates of the intervention effect. If the estimates were similar, then we assumed that any small-study effects had little effect on the intervention effect estimate. If the random-effects estimate was more beneficial, we re-evaluated whether it was reasonable to conclude that the intervention was more effective in the smaller studies. If the larger studies tend to be those conducted with greater methodological rigour, or conducted in circumstances more typical of the use of the intervention in practice, then we reported the results of meta-analyses restricted to the larger, more rigorous studies. Based on the clinical heterogeneity, we expected that several analyses would display statistical between-trial heterogeneity (I^2 greater than 0%). For random-effects models, precision decreased with increasing heterogeneity and CIs would widen correspondingly. Therefore, we expected that the random-effects model would give the most conservative (and a more correct) estimate of the intervention effect. Accordingly, we planned to report the results of our analyses based on random-effects meta-analyses.

Trial Sequential Analysis

We performed Trial Sequential Analysis to evaluate the risk of type 1 and type 2 errors (TSA 2011; Wetterslev 2017), and to evaluate futility in the analyses of our primary outcomes (Higgins 2008). We defined the required information size (also known as the 'heterogeneity adjusted required information size' (DARIS)) as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and assumed control risk (ACR). We defined firm evidence as established if the Z-curve crossed the monitoring boundary (also known as the 'trial sequential monitoring boundary') before reaching the required information size. We constructed futility boundaries to evaluate the uncertainty of obtaining a chance neutral finding. We performed the analyses with alpha set to 3%, power to 90%, and model-based diversity. We planned to conduct the analyses including all randomised clinical trials and limited to trials at low risk of bias. We only undertook analyses including all trials due to the small number of trials at low risk of bias. We planned to estimate the RRR based on the upper CI for outcomes with a potential beneficial effect and the ACR in the pair-wise meta-analysis: for mortality, we used an RRR of 18% and an ACR of 5% (diversity 0%); for hepatic encephalopathy, we used an RRR set to 17% and an ACT of 40% (diversity 78%); for serious adverse events, we used an RRR of 10% and an ACR of 10% (diversity 0%). Due to the limited statistical power of our analyses, we also undertook post-hoc Trial Sequential Analyses using an assumed RRR of 25% for the outcomes mortality and serious adverse events.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analyses to investigate heterogeneity based on stratification of trials by risk of bias and the type of hepatic encephalopathy overt (acute (episodic/recurrent) or chronic); minimal, and primary prevention. We also compared randomised clinical trials evaluating intravenous or oral L-ornithine L-aspartate and compared randomised clinical trials by publication status. Subgroup differences were analysed based on the variation (interaction) between different populations of participants or trials, using the test for subgroup differences (Chi^2 and I^2 values).

Sensitivity analysis

We performed sensitivity analyses excluding randomised clinical trials that included participants with iatrogenic shunts, and planned to conduct worst-case and best-case scenario analyses if we had access to the necessary data (number of participants with missing outcome data in both allocation groups).

'Summary of findings' tables

We used GRADEpro to generate 'Summary of findings' tables with information about all primary and secondary outcomes, risk of bias, and results of the meta-analyses (Brozek 2008). We used the GRADE system to evaluate the quality of the evidence for outcomes reported in the review (Brozek 2008), considering the within-trial risk of bias, inconsistency, imprecision, indirectness, and publication bias. We included the information in the interpretation of our results and reported conclusions based on the 'EPICOT' principle (Brown 2006).

RESULTS

Description of studies

We identified 36 randomised clinical trials which potentially fulfilled our inclusion criteria (Characteristics of included studies table; Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Schmid 2010; Abid 2011; Blanco Vela 2011c; Mittal 2011; Ndraha 2011; Hasan 2012; Zhou 2013; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018).

We excluded 20 studies because they were quasi-randomised, observational, included participants with acute liver failure, were not controlled, or for other reasons (Characteristics of excluded studies table; Müting 1980; Reikowski 1982; Merz 1988e; Merz 1991; Merz 1992b; Staedt 1993; Rees 2000; Delcker 2002; Acharya 2009; Abdo-Francis 2010; Lim 2010; Ndhara 2010; Ong 2011; Tenda 2012; McPhail 2013; Aidrus 2015; Badea 2015; Popa 2015; Tiller 2016; Grover 2017).

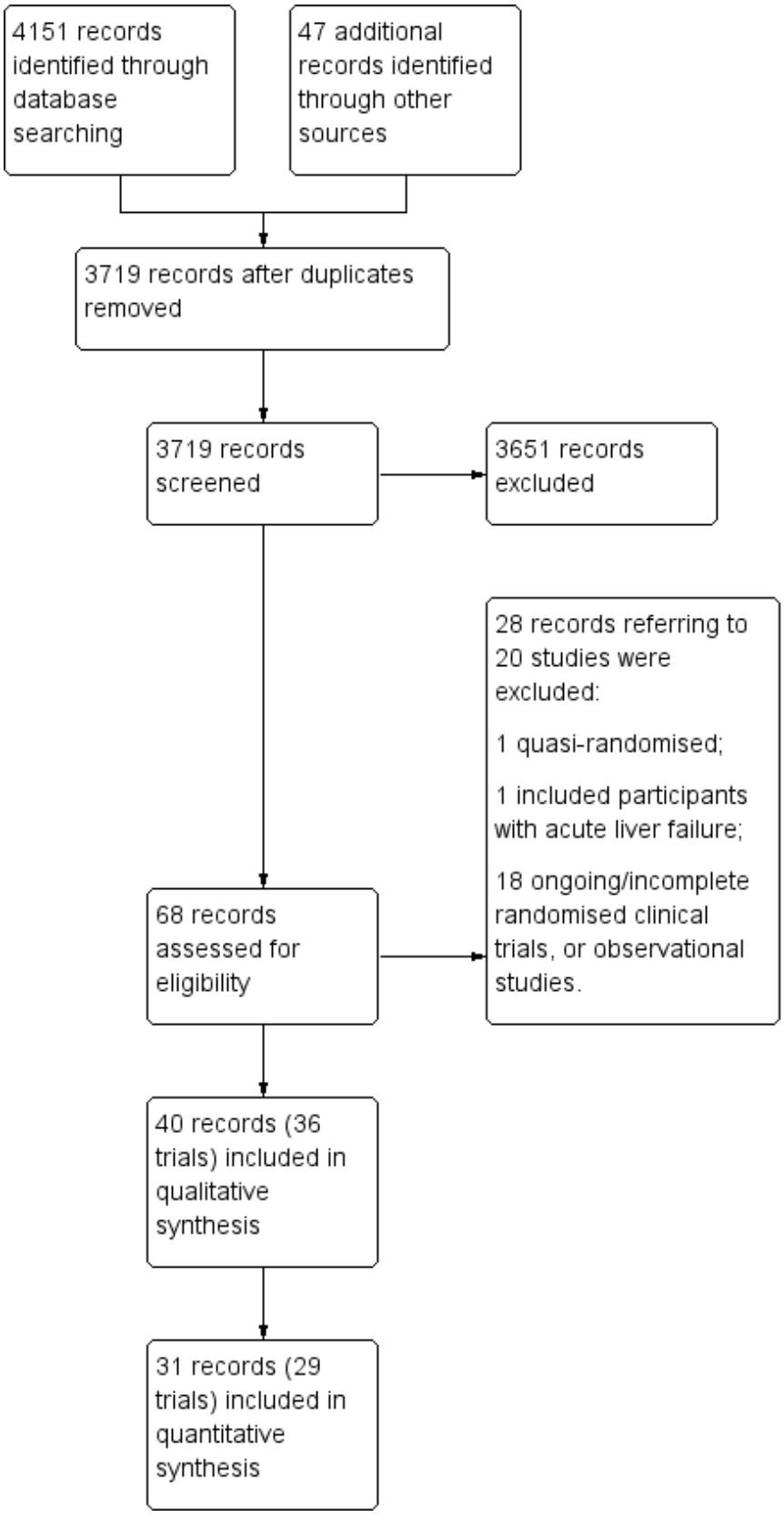
We identified no ongoing studies.

Results of the search

We identified 4151 potentially relevant references from electronic databases and 47 additional records through manual searches and enquiries (Figure 1). We removed duplicates and references that did not refer to publications relevant to this review (e.g. publications describing animal studies), leaving 68 reports for further assessment. Included within these 68 were reports of 13 trials (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1988e; Merz 1989a; Merz 1989b; Merz 1991; Merz 1992a; Merz 1992b; Merz 1994a; Merz 1994b), from an unpublished report of a meta-analysis of studies undertaken between 1986 and 1999 by

Merz Pharmaceuticals or an oral presentation of a meta-analysis of published and unpublished trials given at the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) 2017 meeting by a Merz representative (or both Merz Pharmaceuticals and ISHEN). Of these, we excluded three trials that were not randomised or did not appear to include participants with cirrhosis or hepatic encephalopathy (Merz 1988e; Merz 1991; Merz 1992b; Characteristics of excluded studies table). A further 25 reports describing 17 trials were excluded for a variety of reasons. In total, we identified 40 records describing 36 randomised clinical trials, which fulfilled our inclusion criteria (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Schmid 2010; Abid 2011; Blanco Vela 2011c; Mittal 2011; Ndraha 2011; Hasan 2012; Zhou 2013; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018).

Figure 1. Study flow diagram.



We were unable to gather outcome data from four randomised clinical trials, involving 317 participants, which were only published as abstracts and for which, despite enquiry, no further information was forthcoming (Fleig 1999; Maldonado 2010; Oruc 2010; Hasan 2012). We were also unable to obtain outcome data from three of the remaining ten unpublished trials, involving at least 169 participants (Merz 1988d; Merz 1994a; Merz 1994b). Accordingly, our qualitative analyses included 36 randomised clinical trials while our quantitative analyses included 29 randomised clinical trials (Figure 1).

Included studies

Sixteen randomised clinical trials were published as full paper articles (Feher 1997; Kircheis 1997; Stauch 1998; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Schmid 2010; Abid 2011; Mittal 2011; Ndraha 2011; Zhou 2013; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Sidhu 2018), 10 as abstracts (Fleig 1999; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Blanco Vela 2011c; Hasan 2012; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017), and 10 were unpublished (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b). We received information from investigators about the methods and outcomes for seven of the included randomised clinical trials (Abid 2011; Blanco Vela 2011c; Mittal 2011; Bai 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Sidhu 2018). We also received an unpublished report from Merz Pharmaceuticals and information from a Merz-sponsored presentation of published and unpublished studies which provided information on 10 additional unpublished randomised clinical trials (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b).

The countries of origin of the included trials, where known, were China (Hong 2003; Chen 2005; Zhou 2013; Bai 2014), Germany (Merz 1988b; Merz 1988c; Merz 1989a; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999), India (Puri 2010; Mittal 2011; Sharma 2014; Varakanahalli 2017; Sidhu 2018), Mexico (Poo 2006; Maldonado 2010; Blanco Vela 2011c; Higuera-de la Tijera 2017), Indonesia (Ndraha 2011; Hasan 2012), Pakistan (Ahmad 2008; Abid 2011), Austria (Schmid 2010), Brazil (Alvares-da-Silva 2014), Thailand (Nimanong 2010), Turkey (Oruc 2010), and the UK (Taylor-Robinson 2017).

Participants

The total number of registered participants was at least 2377. Seven randomised clinical trials included participants with acute, overt hepatic encephalopathy (Chen 2005; Ahmad 2008; Nimanong 2010; Oruc 2010; Blanco Vela 2011c; Zhou 2013; Sidhu 2018), one evaluated participants with chronic hepatic encephalopathy (Poo 2006), seven evaluated minimal hepatic encephalopathy (Hong 2003; Maldonado 2010; Puri 2010; Mittal 2011; Ndraha 2011; Alvares-da-Silva 2014; Sharma 2014), and four evaluated participants with no previous hepatic encephalopathy (Feher 1997; Bai 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017). One trial looked at the prevention of recurrence of hepatic encephalopathy (Varakanahalli 2017). The remaining randomised clinical trials evaluated participants with acute, overt, or minimal hepatic encephalopathy (Abid 2011), participants with chronic, overt, or minimal hepatic encephalopathy (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Kircheis 1997; Stauch 1998; Fleig 1999; Schmid 2010; Hasan 2012), or participants with minimal or no previous hepatic encephalopathy (Taylor-Robinson 2017). Information on the type of hepatic encephalopathy could not be obtained for two of the unpublished randomised clinical trials (Merz 1988d; Merz 1994a).

Interventions

Thirty-six randomised clinical trials compared L-ornithine L-aspartate with either placebo (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Ahmad 2008; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Schmid 2010; Abid 2011; Hasan 2012; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018), or no intervention (Hong 2003; Chen 2005; Mittal 2011; Ndraha 2011; Zhou 2013). Six randomised clinical trials included control groups allocated to lactulose (Merz 1994b; Poo 2006; Blanco Vela 2011c; Mittal 2011; Higuera-de la Tijera 2017), probiotics (Mittal 2011; Sharma 2014), or rifaximin (Sharma 2014; Higuera-de la Tijera 2017).

Eighteen trials evaluated intravenous L-ornithine L-aspartate (Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1992a; Merz 1994b; Feher 1997; Kircheis 1997; Fleig 1999; Chen 2005; Ahmad 2008; Oruc 2010; Schmid 2010; Abid 2011; Blanco Vela 2011c; Zhou 2013; Bai 2014; Sidhu 2018); the daily dose of intravenous L-ornithine L-aspartate ranged from 10 g to 40 g (median 20 g), while the duration of treatment ranged from three to 35 days (median eight days). Eighteen trials evaluated oral L-ornithine L-aspartate (Merz 1987; Merz 1988a; Merz 1989b; Merz 1994a; Stauch 1998; Hong 2003; Poo 2006; Maldonado 2010; Nimanong 2010; Puri 2010; Mittal 2011; Ndraha 2011; Hasan 2012; Alvares-da-Silva 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017); the daily dose of oral L-ornithine L-aspartate ranged from 9 g to 18 g (median 17 g), while the duration of treatment ranged from seven to 180 days (median 30 days).

Eighteen randomised clinical trials evaluating intravenous administration included participants with acute (six trials), chronic/minimal hepatic encephalopathy (nine trials), acute/minimal hepatic encephalopathy (one trial), or no previous hepatic encephalopathy (two trials). We were unable to obtain information on the type of hepatic encephalopathy in one trial evaluating intravenous administration (Merz 1988d). The 18 randomised clinical trials evaluating orally administered L-ornithine L-aspartate included participants with acute (one trial), chronic (one trial), minimal (seven trials), chronic/minimal (six trials), minimal/no previous hepatic encephalopathy (one trial), no previous hepatic encephalopathy (one trial), or no current hepatic encephalopathy (one trial).

Outcomes

The total number of participants included in our quantitative analyses was 1891. We did not have access to outcome data for quantitative analyses from seven randomised clinical trials with at least 486 participants, corresponding to at least 20.4% of the total number of registered participants (Merz 1988d; Merz 1994a; Merz 1994b; Fleig 1999; Maldonado 2010; Oruc 2010; Hasan 2012). The duration of follow-up ranged from three days to one month in randomised clinical trials evaluating intravenous administration and from seven to 180 days in trials evaluating oral administration.

The tests used to evaluate hepatic encephalopathy and to define improved manifestations varied (Characteristics of included studies table). Commonly used scales included the West-Haven criteria (Conn 1977), and the Portal Systemic Encephalopathy Score & Index that combines an evaluation of mental status with the scored severity of asterixis, Number Connection Test-A results, electroencephalograph mean cycle frequency, and blood ammonia concentration (Conn 1977). Number Connection Test-A was the most commonly employed single psychometric test.

Excluded studies

We excluded 20 clinical trials (Characteristics of excluded studies table; Müting 1980; Reikowski 1982; Merz 1988e; Merz 1991; Merz 1992b; Staedt 1993; Rees 2000; Delcker 2002; Acharya 2009; Abdo-Francis 2010; Lim 2010; Ndhara 2010; Ong 2011; Tenda 2012; McPhail 2013; Aidrus 2015; Badea 2015; Popa 2015; Tiller 2016; Grover 2017).

One of the excluded studies was an open quasi-randomised trial, which compared an intravenous infusion of L-ornithine L-aspartate with placebo (saline solution) (Aidrus 2015). The investigators used hospital admission numbers in the allocation of participants to intervention (even numbers) or placebo (uneven numbers). The study included 102 participants with cirrhosis due to viral hepatitis and acute, overt (Grade II to IV) hepatic encephalopathy. None died or experienced adverse events.

One randomised clinical trial included participants with acute liver failure (Acharya 2009). The trial evaluated intravenous L-ornithine L-aspartate 30 g/day (102 participants) versus placebo (99 participants). The trial report included per-protocol analyses. Of the 185 participants analysed, 31 died in the treatment group and 39 died in the placebo group. Overall, there was no beneficial or harmful effects of L-ornithine L-aspartate on mortality, cerebral oedema, grade of encephalopathy, degree of prolongation of the prothrombin time, serum aspartate aminotransferase activity, or blood ammonia concentrations.

Three trials were identified in an unpublished report of a meta-analysis of intravenous L-ornithine L-aspartate trials conducted between 1988 and 1999 undertaken by Merz Pharmaceuticals (Delcker 2000b), or in a meta-analysis of published and unpublished trials presented at an international meeting in 2017 by a Merz representative. One trial was not randomised or blinded (Merz 1988e), and two were not randomised or controlled (Merz 1991; Merz 1992b) (Characteristics of excluded studies table).

One randomised clinical trial, involving 32 participants with minimal hepatic encephalopathy, evaluated oral L-ornithine L-aspartate 3.7 g together with branched-chain amino acids given as a supplement either during the daytime or late evening (Tenda 2012). There were no differences in clinical outcome after one month; there were no serious adverse events.

We excluded a case series involving people with cirrhosis and acute variceal bleeding given lactulose with or without L-ornithine L-aspartate (Badea 2015), and nine observational studies involving participants with cirrhosis and overt (Reikowski 1982; Delcker 2002; Abdo-Francis 2010; Lim 2010; Ong 2011; Popa 2015; Tiller 2016), or minimal hepatic encephalopathy (Ndhara 2010; Grover 2017). Three additional observational studies evaluated the effect of L-ornithine L-aspartate on cerebral magnetic imaging and spectroscopy in people with previous minimal hepatic encephalopathy (McPhail 2013), on portal vein blood ammonia levels following a glutamine challenge (Rees 2000), or the effects of a surgically created portal systemic shunt (Müting 1980). Finally, we excluded one dose-finding study that evaluated the dose-dependent effects of ornithine aspartate on postprandial hyperammonaemia and plasma amino acids (Staedt 1993). None of the excluded studies reported serious adverse events.

Risk of bias in included studies

We carried out the risk of bias assessment based on the information retrieved from the publications and from investigators (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

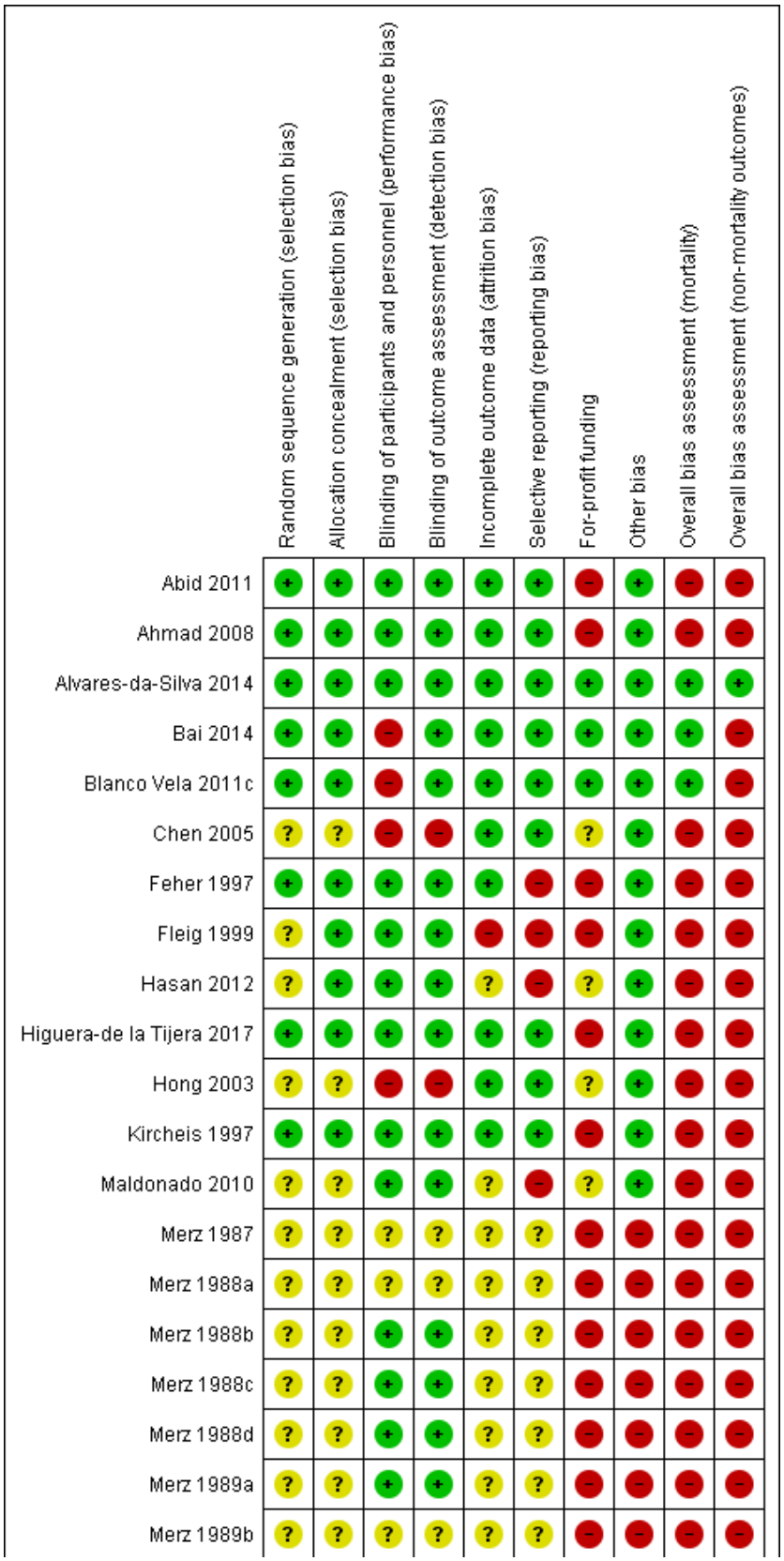
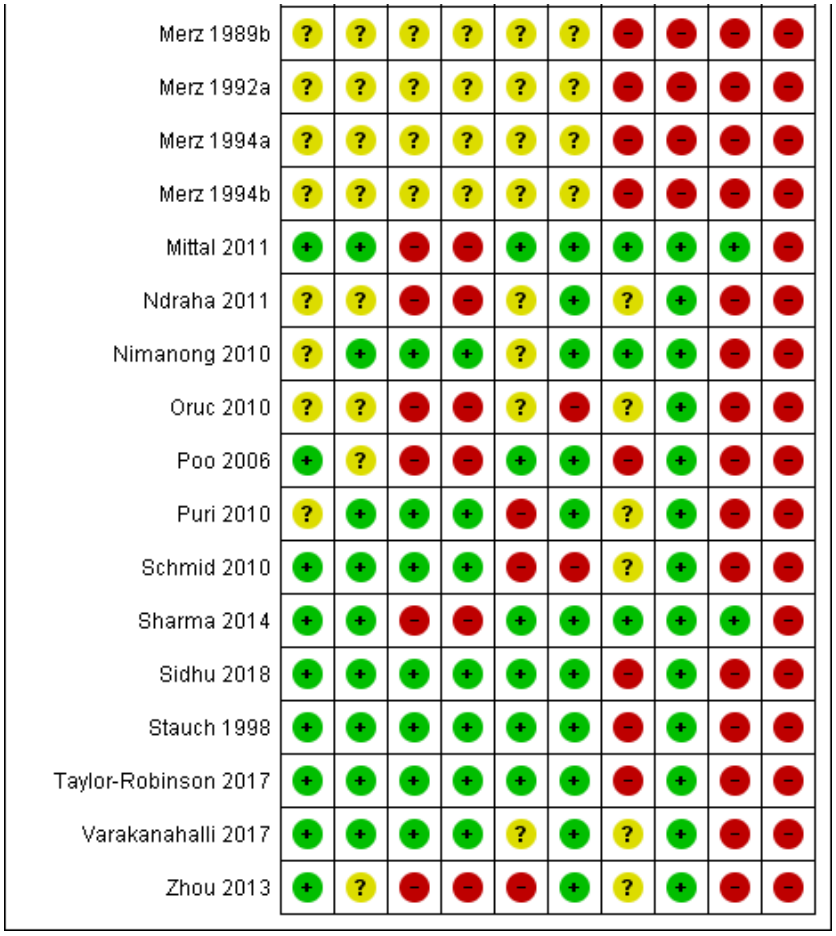


Figure 2. (Continued)



Allocation

Investigators in 15 of the included randomised clinical trials used a computer or table to generate the allocation sequence and concealed the allocation using central randomisation or administration of serially numbered opaque sealed envelopes or coded drug containers (low risk of bias; Feher 1997; Kircheis 1997; Stauch 1998; Ahmad 2008; Schmid 2010; Abid 2011; Blanco Vela 2011c; Mittal 2011; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018). In the remaining trials, investigators did not report how they generated the allocation sequence or concealed the allocation (unclear risk of bias; Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Fleig 1999; Hong 2003; Chen 2005; Poo 2006; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Ndraha 2011; Hasan 2012; Zhou 2013).

Blinding

Twenty randomised clinical trials were double blind with adequate blinding of participants, personnel, and outcome assessors by use of a placebo (low risk of bias; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Ahmad 2008; Maldonado 2010; Nimanong 2010; Puri 2010; Schmid 2010; Abid 2011; Hasan 2012; Alvares-da-Silva 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018). Two trials (Blanco Vela 2011c; Bai 2014) were not blinded to personnel/participants, but the outcome assessment was blinded (high risk of performance but low risk of outcome assessment bias). Fourteen trials were open without blinding (high risk of bias: Hong 2003; Chen 2005; Poo 2006; Oruc 2010; Mittal 2011; Ndraha 2011; Zhou 2013; Sharma 2014) or did not report blinding measures (unclear risk of bias: Merz 1987; Merz 1988a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b). Overall, we classified 20 trials as at low risk, 10 trials as at high risk and 6 trials as at unclear risk of performance and detection bias.

Incomplete outcome data

Sixteen included randomised clinical trials had no missing outcome data and all participants were included in the analyses or else if outcome data were missing, data intention-to-treat analyses were undertaken using last observation carried forward (low risk of bias; Feher 1997; Kircheis 1997; Stauch 1998; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Abid 2011; Blanco Vela 2011c; Mittal 2011; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Sidhu 2018). Sixteen randomised clinical trials did not describe or reported incomplete outcome data (unclear risk of bias; Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Maldonado 2010; Nimanong 2010; Oruc 2010; Ndraha 2011; Hasan 2012; Varakanahalli 2017). The remaining four randomised clinical trials specifically excluded participants from

the analyses (high risk of bias; Fleig 1999; Puri 2010; Schmid 2010; Zhou 2013).

Selective reporting

We classed 20 trials as having a low risk of selective reporting bias because they provided data on mortality, hepatic encephalopathy, and serious adverse events or reported clinically relevant outcomes as predefined in protocols (Kircheis 1997; Stauch 1998; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Nimanong 2010; Puri 2010; Abid 2011; Blanco Vela 2011c; Mittal 2011; Ndraha 2011; Zhou 2013; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018). The remaining 16 randomised clinical trials did not report or had incomplete data on mortality or hepatic encephalopathy (unclear risk of bias: Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; high risk of bias: Feher 1997; Fleig 1999; Maldonado 2010; Oruc 2010; Schmid 2010; Hasan 2012).

For-profit funding

Six randomised clinical trials did not receive funding or any other support from pharmaceutical companies (low risk of bias; Nimanong 2010; Blanco Vela 2011c; Mittal 2011; Alvares-da-Silva 2014; Bai 2014; Sharma 2014). Ten randomised clinical trials did not provide information on funding from this source (unclear risk of bias; Hong 2003; Chen 2005; Maldonado 2010; Oruc 2010; Puri 2010; Schmid 2010; Ndraha 2011; Hasan 2012; Zhou 2013; Varakanahalli 2017). Seventeen randomised clinical trials received funding and other support from pharmaceutical companies (high risk of bias; Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Ahmad 2008; Abid 2011; Taylor-Robinson 2017); a further three trials received a supply of L-ornithine L aspartate/ placebo but no other support (high risk of bias; Poo 2006; Higuera-de la Tijera 2017; Sidhu 2018)

Other potential sources of bias

We classed 10 unpublished randomised clinical trials at high risk of other biases (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b), and the remaining trials at low risk of bias for this domain (Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Schmid 2010; Abid 2011; Blanco Vela 2011c; Mittal 2011; Ndraha 2011; Hasan 2012; Zhou 2013; Alvares-da-Silva 2014; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018).

Overall bias assessment

In the assessment of mortality, we classed five randomised clinical trials at low risk of bias (Blanco Vela 2011c; Mittal 2011; Alvares-da-Silva 2014; Bai 2014; Sharma 2014), and the remaining trials at high risk of bias (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Schmid 2010; Abid 2011; Ndraha 2011; Hasan 2012; Zhou 2013; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018).

In the assessment of non-mortality outcomes, we classified one randomised clinical trials at low risk of bias (Alvares-da-Silva 2014); the remaining randomised clinical trials were at high risk of bias (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Hong 2003; Chen 2005; Poo 2006; Ahmad 2008; Maldonado 2010; Nimanong 2010; Oruc 2010; Puri 2010; Schmid 2010; Abid 2011; Blanco Vela 2011c; Mittal 2011; Ndraha 2011; Hasan 2012; Zhou 2013; Bai 2014; Sharma 2014; Higuera-de la Tijera 2017; Taylor-Robinson 2017; Varakanahalli 2017; Sidhu 2018).

Effects of interventions

See: **Summary of findings for the main comparison** L-ornithine L aspartate compared to placebo or no intervention for people with cirrhosis and hepatic encephalopathy; **Summary of findings 2** L-ornithine L-aspartate compared to lactulose for people with cirrhosis and hepatic encephalopathy; **Summary of findings 3** L-ornithine L-aspartate compared to probiotic for people with cirrhosis and hepatic encephalopathy; **Summary of findings 4** L-ornithine L-aspartate compared to rifaximin for people with cirrhosis and hepatic encephalopathy

L-ornithine L-aspartate versus placebo or no intervention

Primary outcomes

Mortality

We identified 33 randomised clinical trials with 2026 participants allocated to L-ornithine L-aspartate versus placebo or no intervention. We were able to extract mortality data from 19 randomised clinical trials involving 1489 participants (Analysis 1.1). Random-effects meta-analysis showed that L-ornithine L-aspartate was associated with a lower risk of mortality when including all trials (RR 0.42, 95% CI 0.24 to 0.72; I^2 = 0%), but not when the analysis was restricted to the four trials at low risk of bias (RR 0.47, 95% CI 0.06 to 3.58; 244 participants) (Analysis 1.1). Regression analysis (P = 0.28) and an inspection of the funnel plot showed no evidence of small-study effects (Figure 3). The Trial Sequential Analysis including all trials (relative risk ratio 18% and assumed control risk 5%) ignored the monitoring boundary and found insufficient evidence to support or refute an effect of L-ornithine L-aspartate on mortality. Post-hoc Trial Sequential Analyses with the RRR increased to 25% found no evidence to support or refute an effect of L-ornithine L-aspartate on this outcome (TSA-adjusted RR 0.42; 95% CI 0.04 to 3.86; Figure 4).

Figure 3. Funnel plot of comparison: 1 L-ornithine L-aspartate versus placebo/no intervention, outcome: 1.1 Mortality.

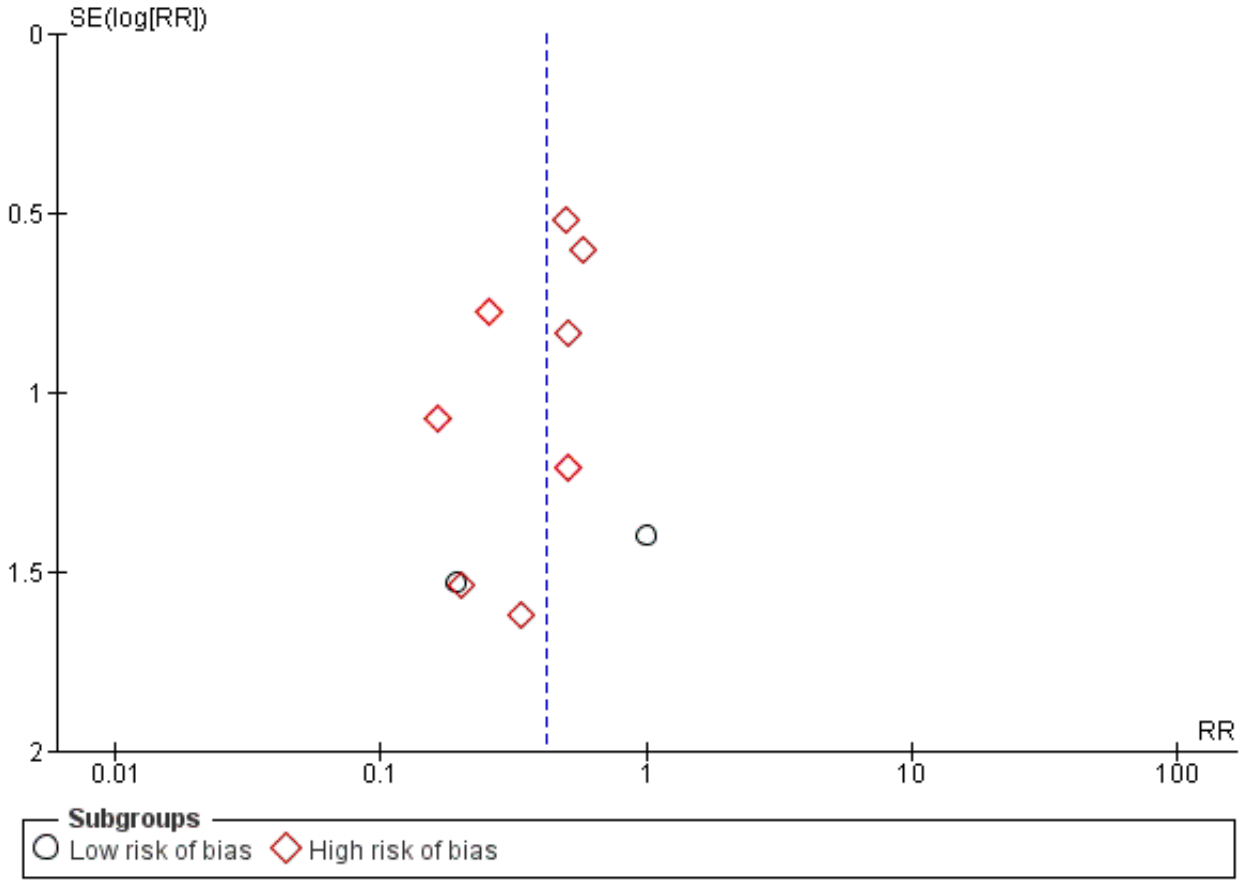
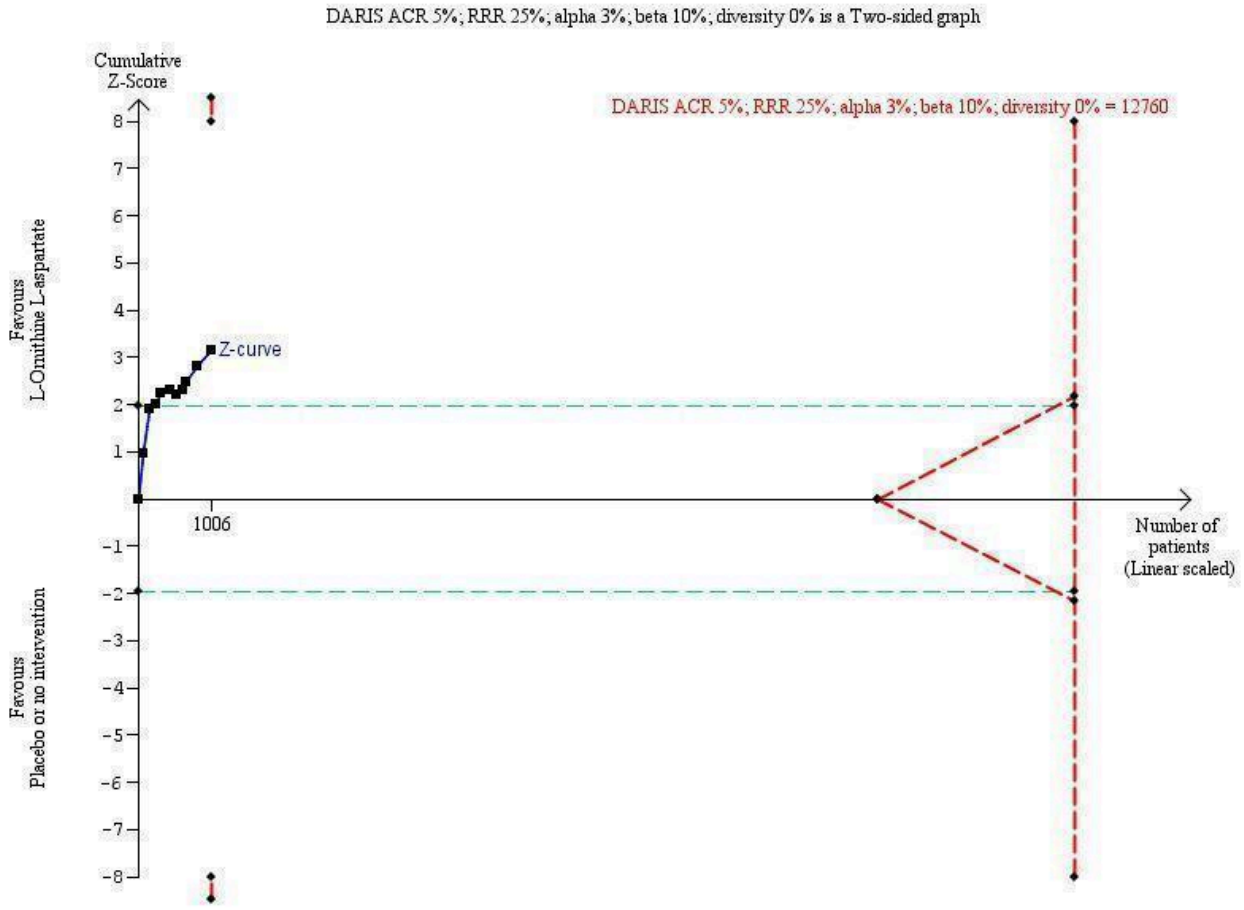


Figure 4. Mortality: Trial Sequential Analysis (relative risk random-effects model) including randomised clinical trials comparing L-ornithine L-aspartate versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. The pair-wise meta-analysis included 19 trials with 1489 participants and found a risk ratio (RR) of 0.42 (95% CI 0.24 to 0.72). The figure shows the Trial Sequential Analysis made with the required information size (also known as the 'heterogeneity adjusted required information size' (DARIS)) defined as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and assumed control risk (ACR). The analysis was made with alpha 3%, power 90%, model-based diversity (0%), RRR 25%, and ACR 5%.

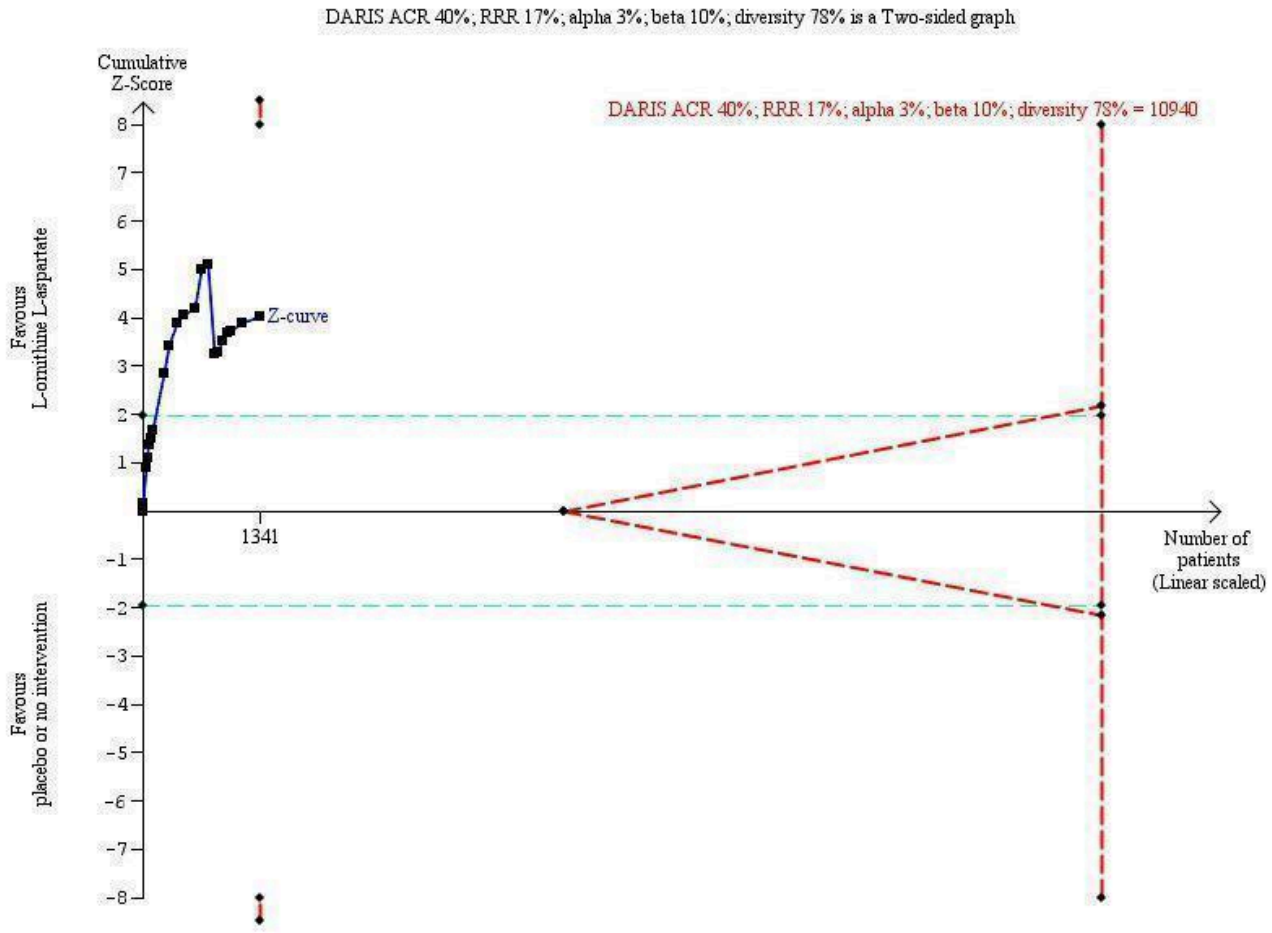


Subgroup analyses showed no difference in the effect of L-ornithine L-aspartate on mortality in trials evaluating acute hepatic encephalopathy, chronic hepatic encephalopathy (no events occurred), minimal hepatic encephalopathy, or the prevention of hepatic encephalopathy (Test for subgroup differences: Chi^2 = 0.63, P = 0.73, I^2 = 0%; Analysis 1.2). Similarly, there were no differences in the effects of L-ornithine L-aspartate when administered intravenously or orally (Test for subgroup differences: Chi^2 = 0.433, P = 0.51, I^2 = 0%; Analysis 1.3), or between trials published as full articles, or in abstract form (Pooled effect: Chi^2 = 0.04, P = 0.85, I^2 = 0%; Analysis 1.4).

Hepatic encephalopathy

We extracted data on hepatic encephalopathy from 22 trials involving 1375 participants (Analysis 1.5). The random-effects meta-analysis suggested a beneficial effect favouring L-ornithine L-aspartate when including all trials, but the between-trial heterogeneity was substantial (RR 0.70, 95% CI 0.59 to 0.83; I^2 = 62%); there was no beneficial effect in the one trial at low risk of bias (RR 0.96, 95% CI 0.85 to 1.07; 63 participants). Regression analysis and visual inspection of a funnel plot showed no evidence of small-study effects (P = 0.23). The Trial Sequential Analysis (relative risk ratio 17%, assumed control risk 40%, alpha 3% and power 90%; diversity 50%) ignored trials in interim analyses and found that the Z-curve crossed the monitoring boundary when including all trials regardless of bias control (TSA adjusted RR 0.75; 95% CI 0.35 to 1.42; Figure 5).

Figure 5. Hepatic encephalopathy: Trial Sequential Analysis of hepatic encephalopathy (relative risk random-effects model). The analysis included randomised clinical trials comparing L-ornithine L-aspartate versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. The pair-wise meta-analysis included 1375 participants and 22 trials and found a risk ratio (RR) of 0.70 (95% CI 0.59 to 0.83). The figure shows the Trial Sequential Analysis made with the required information size (also known as the 'heterogeneity adjusted required information size' (DARIS)) defined as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and assumed control risk (ACR). The analysis was made with alpha 3%, power 90%, model-based diversity (78%), RRR 17%, and ACR 40%.



Subgroup analyses found no difference in the effect of L-ornithine L-aspartate on hepatic encephalopathy in trials evaluating acute hepatic encephalopathy, chronic hepatic encephalopathy, minimal hepatic encephalopathy, or the prevention of hepatic encephalopathy (Test for subgroup differences: $Chi^2 = 7.15$, $P = 0.07$, $I^2 = 58\%$; Analysis 1.6).

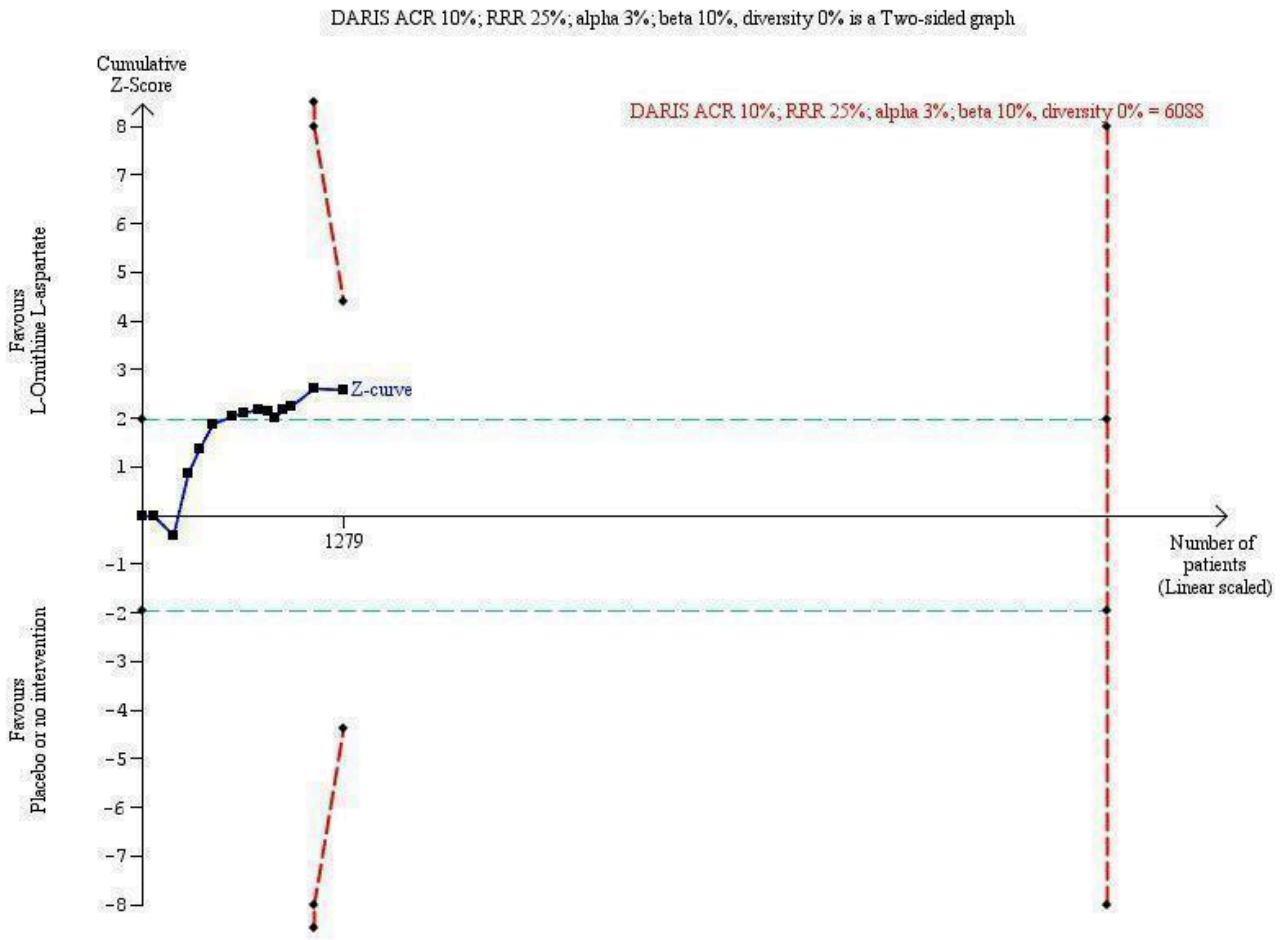
There was no subgroup difference in effect on hepatic encephalopathy between trials evaluating L-ornithine L-aspartate given intravenously or orally (Test for subgroup differences $Chi^2 = 0.26$, $P = 0.61$, $I^2 = 0\%$; Analysis 1.7). Subgroup analysis based on publication status showed a potential difference between trials published as full articles or abstracts and those that were unpublished (Test for subgroup differences: $Chi^2 = 6.78$, $P = 0.03$, $I^2 = 70.5\%$; Analysis 1.8). Additional subgroup analyses found no difference between trials with complete or incomplete data (Test for subgroup differences: $Chi^2 = 2.19$, $P = 0.14$, $I^2 = 54.4\%$; Analysis 1.9).

Serious adverse events

We were able to extract data on serious adverse events from 19 published randomised clinical trials with 1489 participants (Analysis 1.10). Random-effects meta-analysis showed that L-ornithine L-aspartate was associated with a lower risk of serious adverse events when including all trials (RR 0.63, 95% CI 0.45 to 0.90; 19 trials; 1489 participants; $I^2 = 0\%$); there was no beneficial effect in the one trial at low risk of bias (RR 0.83, 95% CI 0.15 to 4.65; 63 participants). Regression analysis found no small-study effects ($P = 0.989$). The Trial Sequential Analysis (relative risk ratio 3% and assumed control risk 10%) ignored the monitoring boundary due to insufficient information and found no evidence to support or refute an effect of L-ornithine L-aspartate on serious adverse events. Post-hoc subgroup analyses with the RRR increased to 25% found no evidence to support or refute an effect of L-ornithine L-aspartate (TSA adjusted RR 0.63; 95% CI 0.32 to 1.24; Figure 6). Subgroup analyses found no difference between trials evaluating acute or chronic hepatic encephalopathy, minimal hepatic encephalopathy,

or the prevention of hepatic encephalopathy (Test for subgroup differences: Chi^2 = 1.13, P = 0.77, I^2 = 0%; Analysis 1.11). There was no difference between trials evaluating intravenous or oral administration (Test for subgroup differences: Chi^2 = 0.25, P = 0.62, I^2 = 0%; Analysis 1.12), or between trials published as full-paper articles or abstracts, or those that were unpublished (Test for subgroup differences: Chi^2 = 1.14, P = 0.23, I^2 = 30.7%; Analysis 1.13).

Figure 6. Serious adverse events: Trial Sequential Analysis (relative risk random-effects model) including randomised clinical trials comparing L-ornithine L-aspartate versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. The pair-wise meta-analysis includes 19 trials with 1489 participants and found a RR of 0.63 (95% CI 0.45 to 0.90). The figure shows the Trial Sequential Analysis made with the required information size (also known as the 'heterogeneity adjusted required information size' (DARIS)) defined as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and assumed control risk (ACR). The analysis is made with alpha 3%, power 90%, model-based diversity (0%), RRR 25%, and ACR 10%.



Secondary outcomes

We were unable to conduct meta-analyses evaluating health-related quality of life. Three randomised clinical trials evaluated this outcome. The first evaluated quality of life in people with minimal hepatic encephalopathy using the Liver Disease Quality of Life Assessment (Alvares-da-Silva 2014), which includes scores for symptoms of liver disease, effects of liver disease, concentration, memory, quality of social interaction, health distress, sexual problems, sleep, loneliness, hopelessness, and stigma of liver disease. There were no differences in health-related quality of life in participants allocated to L-ornithine L-aspartate at the beginning or end of the six-month study period. The second trial evaluated quality of life in people with minimal hepatic encephalopathy using the Sickness Impact Profile questionnaire in a four-way comparison of no treatment, L-ornithine L-aspartate, rifaximin, and probiotics (Mittal 2011). At the end of three months, the total Sickness Impact Profile score decreased by 1.05 in the no treatment group, by 7.33 in the L-ornithine L-aspartate group (P < 0.001), by 6.98 in the lactulose group (P < 0.001), and by 6.24 in the probiotics group (P < 0.001). The decrease in the Sickness Impact Profile score correlated with improvement in minimal hepatic encephalopathy, but on multivariate analysis, there was no correlation with the type of intervention offered, which were considered to be equally effective. The third trial evaluated the Sickness Impact Profile score in people recovering from an episode of acute overt hepatic encephalopathy

randomised to either L-ornithine L-aspartate or placebo for six months for secondary prophylaxis (Varakanahalli 2017). There was a greater decrease in the scores in participants treated with L-ornithine L-aspartate (-7.89) compared with participants receiving the placebo preparation (-0.95) (P = 0.001).

In the analyses of non-serious adverse events, we found no differences between L-ornithine L-aspartate and placebo or no intervention in the overall analysis (RR 1.15, 95% CI 0.75 to 1.77) or when evaluating diarrhoea (RR 1.32, 95% CI 0.07 to 24.18), flatulence (RR 1.60, 95% CI 0.49 to 5.18), headache (RR 7.67, 95% CI 0.39 to 148.82), abdominal pain (RR 0.63, 95% CI 0.23 to 1.69), fever (RR 1.72, 95% CI 0.12 to 23.62), general gastrointestinal effects (RR 0.89, 95% CI 0.55 to 1.45), pruritus (RR 0.60, 95% CI 0.30 to 1.21), or fatigue (RR 0.83, 95% CI 0.58 to 1.18) (Analysis 1.14). L-ornithine L-aspartate increased the risk of nausea/vomiting (RR 2.26, 95% CI 1.25 to 4.10; 10 trials; 639 participants; I^2 = 0%) (Analysis 1.14).

Exploratory outcomes

L-ornithine L-aspartate was associated with a reduction in blood ammonia concentrations in trials reporting the difference between baseline values and values at the end of follow-up (MD -12.94), 95% CI -20.04 to -5.83; 13 trials; 738 participants; I^2 = 74%; Analysis 1.15). Based on the between-trial heterogeneity (I^2 = 98%), we chose to disregard the analysis of trials that only reported blood ammonia concentrations at the end of the treatment period.

L-ornithine L-aspartate versus other active agents

Lactulose

Meta-analyses of four trials with 175 participants showed no difference between L-ornithine L-aspartate and lactulose in relation to mortality when including all trials (RR 0.68, 95% CI 0.11 to 4.17) or when the analysis was restricted to trials at low risk of bias (RR 3.00, 95% CI 0.13 to 71.51; 2 trials; 111 participants) (Analysis 2.1). Likewise, there was no difference between L-ornithine L-aspartate and lactulose for hepatic encephalopathy (RR 1.13, 95% CI 0.81 to 1.57; I^2 = 0%) (Analysis 2.2) and serious adverse events (RR 0.69, 95% CI 0.22 to 2.11; I^2 = 0%) (Analysis 2.3).

We were unable to undertake meta-analyses of non-serious adverse events (Analysis 2.4). Individual trials found no difference between L-ornithine L-aspartate and lactulose in relation to the risk of abdominal pain (RR 0.07, 95% CI 0.00 to 1.13), but lactulose increased the risk of diarrhoea (RR 0.03, 95% CI 0.00 to 0.54), bloating (RR 0.05, 95% CI 0.00 to 0.77), and flatulence (RR 0.05, 95% CI 0.00 to 0.77).

One trial evaluated quality of life based on the 36-item Short Form (SF-36) and EuroQoL questionnaires; there were no significant differences between L-ornithine L-aspartate and lactulose for the total SF-36 score or the subscales, but a greater improvement in the EuroQoL total score in the L-ornithine L-aspartate group (P < 0.05) (Poo 2006).

Based on the between-trial heterogeneity (I^2 = 94%), we chose to disregard the analysis of blood ammonia concentrations (Analysis 2.5). We did not undertake regression analyses, Trial Sequential Analyses, or evaluate funnel plots due to the small number of trials included.

Probiotics

Two trials involving 143 participants assessed L-ornithine L-aspartate versus probiotics and found no beneficial difference in relation to the outcomes mortality (RR 1.01, 95% CI 0.11 to 9.51) (Analysis 3.1), but a possible beneficial effect of L-ornithine L-aspartate on hepatic encephalopathy (RR 0.71, 95% CI 0.56 to 0.90) (Analysis 3.2); there were no beneficial differences in serious adverse events (RR 1.07, 95% CI 0.23 to 4.88) (Analysis 3.3), or in changes in blood ammonia concentrations (RR -2.30 95% CI -6.08, 1.48) (Analysis 3.4). The trials did not evaluate health-related quality of life.

Rifaximin

Two randomised clinical trials, involving 105 participants, compared L-ornithine L-aspartate versus rifaximin and found no difference in mortality (RR 0.33, 95% CI 0.04 to 3.03; I^2 = 0%; Analysis 4.1), hepatic encephalopathy (RR 1.06, 95% CI 0.57 to 1.96; I^2 = 0%) (Analysis 4.2), or serious adverse events (RR 0.32, 95% CI 0.01 to 7.42; Analysis 4.3).

One trial reported on nausea and vomiting and found no difference between the groups (RR 0.32, 95% CI 0.01 to 7.42; Analysis 4.4). The trials did not evaluate health-related quality of life or blood ammonia concentrations.

'Summary of findings' tables

In the analyses comparing L-ornithine L-aspartate versus placebo/no intervention (Summary of findings for the main comparison), we downgraded the quality of the evidence to 'very low' for mortality because the subgroup analysis of the four trials at low risk of bias found no evidence for a beneficial effect and the results were not confirmed in the Trial Sequential Analysis. We downgraded the quality of evidence for hepatic encephalopathy to 'very low' because none of the included trials had a low risk of bias; there was substantial between-study heterogeneity and the Trial Sequential Analysis, which included all trials regardless of bias control, found no evidence to support or refute an intervention effect (Summary of findings for the main comparison). We downgraded the quality of evidence for serious adverse events to 'very low' because only one trial had a low risk of bias and the results were not confirmed in the Trial Sequential Analysis (Summary of findings for the main comparison).

We downgraded the evidence for the secondary outcome health-related quality of life to 'very low' because the two trials that assessed this outcome were at high risk of bias and we were unable to combine the data in an overall analysis. We also downgraded the evidence for non-serious adverse events to 'very low' because only one included trial had a low risk of bias; the CIs were very wide and we were only able to include data from 14 trials in our meta-analysis (Summary of findings for the main comparison).

There were no differences in outcomes in the analyses of the four trials comparing L-ornithine L-aspartate versus lactulose for any of the primary outcomes when considering all trials and the two trials at low risk of bias for the outcome mortality (Summary of findings 2); information on non-serious events adverse events was only available from one trial. Likewise, there were no differences in outcomes in the analyses comparing L-ornithine L-aspartate versus probiotics (Summary of findings 3), or L-ornithine L-aspartate versus rifaximin (Summary of findings 4).

DISCUSSION

Summary of main results

This systematic review included qualitative information from 36 randomised clinical trials, involving at least 2377 participants and quantitative data from 29 randomised clinical trials involving 1891 participants. The primary analyses suggested that use of L-ornithine L-aspartate was associated with a reduction in all-cause mortality, compared with placebo or no intervention, when including all trials, but not when the analysis was restricted to the trials at low risk of bias. In addition, the results were not confirmed in the Trial Sequential Analysis. We found no significant difference in the effect of L-ornithine L-aspatate on mortality when trials were stratified by the type of hepatic encephalopathy or the route of drug administration. Use of L-ornithine L-aspartate was associated with a beneficial effect on hepatic encephalopathy when all randomised trials were considered but not in the one trial at low risk of bias, and the Trial Sequential Analysis was equivocal. We found no significant difference in the effects of L-ornithine L-aspartate on hepatic encephalopathy between trials evaluating acute and chronic hepatic encephalopathy, minimal hepatic encephalopathy, or the prevention of hepatic encephalopathy or in relation to the route of administration. Use of L-ornithine L-aspartate was associated with a reduction in the risk of serious adverse events when all randomised clinical trials were considered, but benefit was not seen in the one trial at low risk of bias or in the Trial Sequential Analysis. There was no benefit with regards to serious adverse events in relation to the route of administration. The quality of the evidence for all three primary outcomes was very low. Three trials assessed quality of life but we were unable to combine the results in a meta-analysis. There was no increased risk of non-serious adverse effects, except for nausea, with L-ornithine L-aspartate. The quality of the evidence for the secondary outcomes was very low. L-ornithine L-aspartate was associated with a significant reduction in blood ammonia concentrations in trials reporting the difference between baseline values and values at the end of follow-up. No beneficial effects of L-ornithine L-aspartate where identified when compared with lactulose or rifaximin, but a possible beneficial effect on hepatic encephalopathy was observed when compared with probiotics, albeit the quality of the evidence was very low.

Overall completeness and applicability of evidence

The main difficulty in undertaking this review was the high proportion of studies reported, often incompletely, as abstracts and the number of identified studies that had not been published and hence were not in the public domain.

We identified an abstract reporting a multicentre German/Swiss/Austrian randomised clinical trial comparing oral L-ornithine L-aspartate with placebo (Fleig 1999), involving 217 participants with cirrhosis and either minimal or low-grade overt hepatic encephalopathy. This trial has not been published as a full paper but some trial data were subsequently included in a published paper critical of the psychometric test battery used to assess neuropsychiatric status in the study population (Kircheis 2007). Kircheis 2007 had access to the trial data and were willing to release them but Merz Pharmaceuticals, who sponsored the trial, did not wish the data to be made available for external distribution.

We also identified an abstract reporting a meta-analysis (Delcker 2000a), using individual patient data, of trials of intravenous L-ornithine L-aspartate against placebo in people with cirrhosis and acute (overt) hepatic encephalopathy. This meta-analysis has not been published as a full paper. We subsequently obtained an incomplete version of an unpublished clinical trial report written by two of the authors of the published abstract, dated October 2000, which had been prepared for Merz Pharmaceuticals (Delcker 2000b). The authors of the report had access to the Merz trials database for L-ornithine L-aspartate and identified 21 pilot studies, feasibility studies, controlled clinical trials, and postmarketing studies, undertaken between 1984 and 1999. Of these, they identified 11 which they thought might be suitable for inclusion in a structured meta-analysis to determine the efficacy and safety of intravenous L-ornithine L-aspartate for the treatment of hepatic encephalopathy in people with cirrhosis. Their ultimate meta-analysis included five randomised, double-blind, placebo-controlled, parallel design clinical trials, involving 246 people with cirrhosis and Grade 0 to II hepatic encephalopathy (Conn 1977), treated for at least seven days. They concluded that participants receiving L-ornithine L-aspartate had a 3.2-fold greater chance (95% CI 1.38 to 7.55) of being free of hepatic encephalopathy at the end of treatment than participants receiving placebo. They also reported that L-ornithine L-aspartate was well tolerated.

Three of the studies included in this internal meta-analysis remain unpublished (Merz 1988b; Merz 1988c; Merz 1989a), while two have been published (Feher 1997 (MRZ 90004-9003); Kircheis 1997 (MRZ 90004-8908)). Six of the 11 trials originally identified in the Merz internal report were excluded from the analyses for a variety of reasons. Two of the six were neither randomised nor controlled (Merz 1991; Merz 1992b), while a third was a dose-finding study (Staedt 1993 (MRZ 90004-8603)); none of these studies would have been eligible for inclusion in our review. However, the remaining three studies excluded from the meta-analysis were eligible and were included (Merz 1988d; Merz 1992a; Merz 1994b). No further information was available on the additional 10 studies mentioned in this report. Negotiations with Merz Pharmaceuticals for release of the additional trial data were unsuccessful.

In early 2017, a representative for Merz Pharmaceuticals presented the result of a meta-analysis of published and unpublished trials of L-ornithine L-aspartate 'for the treatment of hepatic encephalopathy in cirrhosis' at a meeting of the International Society for the Study of Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) in Delhi, India (Butterworth 2017). This presentation provided details of five unpublished placebo-controlled trials of intravenous L-ornithine L-aspartate, involving 152 participants, which were included in the internal Merz clinical trial report (Merz 1988b; Merz 1988c; Merz 1989a; Merz 1992a; Merz 1994b), although not necessarily in the meta-analysis (Delcker 2000a). In addition, information was provided on four unpublished randomised placebo-controlled trials of oral L-ornithine L-aspartate (Merz 1987; Merz 1988a; Merz 1989b; Merz 1994a), and one unpublished non-randomised trial (Merz 1988e).

Thus, we identified 26 unpublished trials and were able, from a combination of the sources mentioned above, to extract some information from 13; 10 of these unpublished trials, involving approximately 287 participants, were included in our analyses (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988d; Merz 1989a; Merz 1989b; Merz 1992a; Merz 1994a; Merz 1994b), while the remaining three were excluded (Merz 1988e; Merz 1991; Merz 1992b). It is possible that we might have excluded some of

the unpublished trials currently considered suitable for inclusion had we had more information. Equally, there may be further unpublished trials that we failed to identify.

Although there were concerns about the volume of unpublished and, to some extent, unavailable trial material, we were still able to include 36 randomised clinical trials involving at least 2377 participants in our qualitative analyses, and 29 randomised clinical trials involving 1899 participants in our quantitative analyses, and we were able to perform meta-analyses for the most important outcomes for people with cirrhosis and hepatic encephalopathy, namely mortality, morbidity, adverse events, and quality of life (Bajaj 2011b). We included information on all of these outcomes, although there was very limited information on quality of life.

The trials evaluated improvement in hepatic encephalopathy using a variety of methods to assess changes in neuropsychiatric status. This partly reflects that the fact that the trials were conducted between 1988 and 2016 during which time diagnostic criteria have changed on more than one occasion. The included trials often used clinical or composite scoring systems and a categorical approach to define improvement (or lack thereof). The diagnostic classification of hepatic encephalopathy also changed during the time period (EASL/AASLD 2014a; EASL/AASLD 2014b). Thus, we decided a priori to utilise the individual primary investigators' classification of the type of hepatic encephalopathy and their outcome criteria as these were likely to have been most clinically relevant at the time. We have provided a comparison of the definition of neuropsychiatric status used in the source material and the current suggested terminology (Table 1). The older trials often used cointerventions such as dietary protein restriction but, although cointerventions were not used consistently in all the trials, participants randomised to experimental or control groups within a given trial would have had equal access to them. This might result in heterogeneity but not in systematic differences between groups.

Hepatic encephalopathy varies widely in its manifestations. The trials included in our review represent the entire spectrum of the syndrome encountered in people with cirrhosis. Thus, we included trials evaluating the use of L-ornithine L-aspartate in people experiencing an acute episode of hepatic encephalopathy, people with chronic hepatic encephalopathy associated with advanced liver disease and/or spontaneous, or surgically created portal-systemic shunts, and people with minimal hepatic encephalopathy who appear clinically normal, but exhibit psychometric and neurophysiological abnormalities or both. In addition, a small number of the trials explored the use of L-ornithine L-aspartate for primary and secondary prophylaxis of hepatic encephalopathy. The fact that the trials addressed all the objectives of the review strengthened the completeness of the evidence. We included all randomised clinical trials with extractable data in our primary analyses. We also conducted subgroup, sensitivity, and regression analyses to determine the differential effects of interventions on the clinical variants.

People with non-cirrhotic portal hypertension and people with fulminant hepatic failure may also develop hepatic encephalopathy but are encountered much less frequently in clinical practice, and are not represented in the included trials. There is no reason to suppose that our results could not be extrapolated to people with hepatic encephalopathy associated with non-cirrhotic portal hypertension (e.g. portal vein block). However, the results may not be directly applicable in people with fulminant hepatic failure.

Episodes of hepatic encephalopathy often develop in response to a precipitating event such as infection, gastrointestinal bleeding, alcohol misuse, or electrolyte disturbances. Identification and treatment of these precipitating factors is key to the management of affected people (EASL/AASLD 2014a; EASL/AASLD 2014b). Avoiding likely precipitants such as constipation, dietary indiscretion, and certain medications can also reduce the risk of developing hepatic encephalopathy in the longer term. It is unclear whether L-ornithine L-aspartate provides additional benefit in situations where hepatic encephalopathy is precipitated by a treatable event. The randomised clinical trials included in our review did not provide detailed information on possible precipitating events, on the effects of interventions designed to ameliorate them, or on the effects, if any, of the addition of L-ornithine L-aspartate.

Hepatic encephalopathy imposes a significant burden on healthcare systems and the resource utilisation associated with the management of people with hepatic encephalopathy is increasing (Poodad 2007). The increased costs do not seem to reflect the duration of hospitalisation, which has decreased, but a combination of direct and indirect factors such as the costs of treatment and rehabilitation after hospitalisation (Neff 2010). None of the randomised clinical trials included in the present review assessed the costs associated with hospitalisation.

Quality of the evidence

The main reasons for downgrading the evidence in this review were bias, imprecision, and potential publication bias.

Bias: we included randomised clinical trials published as full papers or abstracts and obtained additional information on essential aspects of bias control from the authors of these works. In addition, we obtained information on several unpublished trials and were able to obtain some information on these. As recommended, we combined the individual bias domains in an overall assessment (Gluud 2017). We also included an assessment of individual domains, focusing on randomised clinical trials at low risk of selection bias (Higgins 2011; Savovic 2012). We defined mortality, but not serious adverse events, as an outcome that is robust to performance and detection bias (Savovic 2012). This decision can be questioned as lack of blinding is not likely to influence the assessment of events such as variceal bleeding, hepatorenal syndrome, and liver failure. We included any type of for-profit funding as a bias domain (Gluud 2017). The decision to include this domain is debatable (Higgins 2011). The fact that we included gratuitous supply of interventions or placebo was the main reason that we only identified a small number of studies with a low risk of bias in the overall assessment. Based on the assessment of bias control combined with the assessment of the directness of evidence, heterogeneity, precision of effect estimate, and risk of publication bias, we classified the quality of the evidence as very low for the assessment of our primary outcomes mortality, hepatic encephalopathy, and serious adverse events.

Imprecision: where the primary meta-analyses including all trials regardless of bias control, we found potential beneficial effects. However, our Trial Sequential Analyses suggested that we have insufficient evidence to support or refute any beneficial or harmful

effects of this intervention. This suggests that our results may reflect random or systematic errors.

Publication bias: we identified several unpublished trials and trials published in abstract form. Unfortunately, for most of these trials, we either had no data or could only access incomplete data sets. Our analyses of these trials did not show convincing effects of L-ornithine L-aspartate and we, therefore, strongly suspect that publication bias may have affected our findings.

Potential biases in the review process

We undertook the review based on current recommendations for bias control (Higgins 2011; Gluud 2017). One methodological review drew attention to selective inclusion and reporting of outcomes and analyses in systematic reviews (Page 2014). We attempted to minimise possible selection bias by using a comprehensive search strategy that uncovered both published and unpublished trials. Searches in electronic databases were combined with handsearches of the biographies of identified studies. In addition, we searched conference proceedings and abstract books from relevant national and International society meetings. We consider it unlikely that we have missed published trials. In addition, from a starting base of two published abstracts, we identified 26 unpublished trials but could not exclude the possibility that more unpublished trials exist. The selective publication of randomised clinical trials with a positive result increases the risk of outcome reporting bias (Dwan 2008). Our subgroup analysis based on publication status found no differences between published trials or trials with complete data sets and unpublished trials or trials with incomplete data sets for the outcomes mortality and serious adverse events. However, there was a potential difference in relation to publication status for the outcome hepatic encephalopathy not explained by the completeness or otherwise of the data.

Four of the included randomised clinical trials assessed the use of L-ornithine L-aspartate for prevention of hepatic encephalopathy while the remaining 32 trials assessed its use for the treatment of hepatic encephalopathy. All 36 trials were included in the analyses of the primary outcomes and it is possible that combining the prevention and treatment trials in this way may have introduced bias. However, the results of the subgroup analyses showed that the outcomes in the prevention trials were not noticeably different from those in the overall analyses.

Agreements and disagreements with other studies or reviews

Several meta-analyses of the L-ornithine L-aspartate trials have been undertaken (Delcker 2000a; Jiang 2009; Soarez 2009; Perez Hernandez 2011; Bai 2013; Butterworth 2017). The meta-analysis by Delcker 2000a, published in abstract form, included three unpublished and two published studies involving 246 participants (Merz 1988b; Merz 1988c; Merz 1989a; Feher 1997; Kircheis 1997); the meta-analysis found a significant beneficial effect of treatment on the resolution of hepatic encephalopathy, and of the time taken to complete the Number Connection Test and postprandial ammonia concentrations. The meta-analysis by Jiang 2009 included three published randomised clinical trials with 212 participants (Kircheis 1997; Stauch 1998; Poo 2006), and this meta-analysis found that L-ornithine L-aspartate was associated with a beneficial effect on overt, but not minimal, hepatic encephalopathy when compared with placebo or lactulose. The meta-analysis by Soarez 2009 included four placebo-controlled trials with 217 participants (Staedt 1993; Kircheis 1997; Stauch 1998; Rees 2000), and it found that although L-ornithine L-aspartate reduced blood ammonia concentrations, it had no effect on hepatic encephalopathy per se. A subsequent meta-analysis undertaken by Perez Hernandez 2011 included five randomised clinical trials involving 422 participants with cirrhosis (Staedt 1993; Kircheis 1997; Kircheis 2002; Ahmad 2008; Abdo-Francis 2010), and one randomised clinical trial including 201 participants with fulminant liver failure (Acharya 2009). The results showed that L-ornithine L-aspartate improved neuropsychiatric performance and decreased venous blood ammonia concentrations. The meta-analysis by Bai 2013 evaluated eight trials with 646 participants and found that L-ornithine L-aspartate had a beneficial effect in people with overt and minimal hepatic encephalopathy and on fasting ammonia concentrations compared with placebo, no intervention, or lactulose (Kircheis 1997; Stauch 1998; Poo 2006; Ahmad 2008; Schmid 2010; Abid 2011; Mittal 2011; Ndraha 2011). The meta-analyses undertaken in 2011 and 2013 did not adjust the quantitative result by the quality of the evidence. A meta-analysis by Butterworth 2017, published in abstract form, included 16 published and 10 unpublished trials, involving 1618 participants (Merz 1987; Merz 1988a; Merz 1988b; Merz 1988c; Merz 1988e; Merz 1989a; Merz 1989b; Merz 1992a; Staedt 1993; Merz 1994a; Merz 1994b; Feher 1997; Kircheis 1997; Stauch 1998; Fleig 1999; Rees 2000; Chen 2005; Poo 2006; Ahmad 2008; Schmid 2010; Abid 2011; Mittal 2011; Ndraha 2011; Alvares-da-Silva 2014; Bai 2014; Sharma 2014); this meta-analysis found a beneficial effect of L-ornithine L-aspartate on blood ammonia concentrations and mental status . Finally, a meta-analysis (Butterworth 2018), also published in abstract form, included six randomised clinical trials involving 292 people with cirrhosis and minimal hepatic encephalopathy (Kircheis 1997; Stauch 1998; Abid 2011; Mittal 2011; Alvares-da-Silva 2014; Sharma 2014); this meta-analysis found a beneficial effect of L-ornithine L-aspartate on blood ammonia concentrations and also on psychometric performance but only when given orally and not intravenously. The two most recent meta-analyses (Butterworth 2017; Butterworth 2018) were commissioned by Merz Pharmaceuticals, and there are considerable problems with the ascription of bias in the individual trials and in the meta-analyses overall.

In this review, we included 36 trials with at least 2377 participants in our qualitative analyses and 29 randomised clinical trials with 1891 participants in our quantitative analyses, making it the largest and most comprehensive systematic review with meta-analyses undertaken to date. We included both published and unpublished trials and found that L-ornithine L-aspartate may have a beneficial effect on mortality, hepatic encephalopathy, and serious adverse events when compared with placebo or no intervention but that the evidence was of very low quality; we found no beneficial effects of L-ornithine L-aspartate when compared with lactulose or rifaximin, but we found a possible beneficial effect on hepatic encephalopathy when compared with probiotics, albeit the quality of the evidence was very low.

The EASL/AASLD Practice Guidelines state, in relation to L-ornithine L-aspartate, that: "An RCT [randomised clinical trial] on patients with persistent HE [hepatic encephalopathy] demonstrated improvement by IV [intravenous] LOLA [L-ornithine L-aspartate] in psychometric testing and postprandial venous ammonia levels

(Kircheis 1997). Oral supplementation with LOLA is ineffective". It recommends that "IV LOLA can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (Evidence GRADE I, B, 2)" (EASL/AASLD 2014a; EASL/AASLD 2014b). There is no evidence base for these statements.

AUTHORS' CONCLUSIONS

Implications for practice

In this review, we evaluated the efficacy of L-ornithine L-aspartate versus placebo or no interventions from randomised clinical trials for both the prevention and treatment of hepatic encephalopathy in people with cirrhosis. The meta-analyses suggest that L-ornithine L-aspartate may have beneficial effects on mortality, hepatic encephalopathy, and serious adverse events, but the overall quality of this evidence is very low and hence there is considerable uncertainty about these findings.

Implications for research

Our suggested implications for research are provided below following the EPICOT format (Brown 2006).

Evidence (what is the current state of the evidence)? We included 36 randomised clinical trials involving at least 2377 registered participants. There was evidence showing beneficial effects of L-ornithine L-aspartate on mortality, hepatic encephalopathy, and serious adverse events. However, the quality of the evidence was very low, and hence, we are very uncertain about these findings. Further trials are needed.

Participants (what is the population of interest)? We focused on people with cirrhosis and hepatic encephalopathy or people with cirrhosis who were at risk for developing hepatic encephalopathy. Subgroup analyses showed no difference in the effects of L-ornithine L-aspartate when given to prevent hepatic encephalopathy or when used to treat minimal or acute/persistent overt hepatic encephalopathy. Future studies should be designed to look for differences in outcomes in prevention and treatment trials and by type of hepatic encephalopathy. The effects on L-ornithine L-aspartate in people with hepatic encephalopathy and acute liver failure should also be assessed.

Interventions (what are the interventions of interest)? We assessed L-ornithine L-aspartate administered orally or intravenously. We found no difference in the effects of L-ornithine L-aspartate by route of administration. Future studies should look for differences in outcomes by the route of administration.

Comparisons (what are the comparisons of interest)? The included randomised clinical trials provided us with the opportunity to assess L-ornithine L-aspartate against placebo/no intervention, lactulose, rifaximin, and probiotics. Cointerventions were sometimes administered, but these were always given equally to the L-ornithine L-aspartate and comparative groups. Future studies should include comparisons both with placebo/no intervention and other active agents.

Outcomes (what are the outcomes of interest)? The primary outcome measures assessed in this review (mortality, hepatic encephalopathy, and serious adverse events) should be included in all future trials. Health-related quality of life should be included as an outcome variable particularly in people with minimal and chronic persistent hepatic encephalopathy. Blood ammonia concentrations are best assessed as percentage change over trial baseline.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abid 2011

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal (n = 12) or acute (n = 108) hepatic encephalopathy **Mean age ± SD:** L-ornithine L-aspartate 57.1 ± 11.5 years; placebo 57.5 ± 11.0 years **Proportion of men:** L-ornithine L-aspartate 50%; placebo 53% **Aetiology of cirrhosis:** alcohol 4%; hepatitis B 9%; hepatitis C 67%
Interventions	**L-ornithine L-aspartate:** 20 g infused intravenously for 4 hours/day in 250 mL dextrose **Control:** placebo (40 mL distilled water) infused intravenously for 4 hours/day in 250 mL dextrose **Duration of treatment:** 3 days **Cointerventions:** none (participants with infections received antibiotics)
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (assessed using Number Connection Test-A results in participants with minimal and Grade I hepatic encephalopathy and West

Abid 2011 *(Continued)*

	Haven criteria in participants with Grade II-IV hepatic encephalopathy), blood ammonia, serious and non-serious adverse events
Country	Pakistan
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Number Connection Test-A • Venous blood ammonia
Inclusion period	2003 to 2004
Notes	**Publication status:** full-paper article **Unpublished information:** authors provided additional unpublished information via email on 31 October 2015.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. All participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported in trial publication and registered protocol
For-profit funding	High risk	Received an unrestricted grant from Brooks Pharmaceutical
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Ahmad 2008

Methods	Open, parallel-arm, single-centre, placebo-controlled, randomised clinical trial

Ahmad 2008 *(Continued)*

Participants	**Included participants:** cirrhosis and acute, overt hepatic encephalopathy (n = 80) **Mean age ± SD:** L-ornithine L-aspartate 51.7 ± 10.8 years; placebo 52.0 ± 11.7 years **Proportion of men:** 74% **Aetiology of cirrhosis:** alcohol (not reported); hepatitis B/C 96%
Interventions	**L-ornithine L-aspartate:** 20 g infused intravenously for 4 hours/day in 250 mL dextrose **Control:** placebo (40 mL distilled water) infused intravenously for 4 hours/day in 250 mL dextrose **Duration of treatment:** 5 days **Cointerventions:** lactulose, metronidazole
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (improvement defined as improvement in mental state to West Haven criteria grade 0), blood ammonia, serious and non-serious adverse events
Country	Pakistan
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Postprandial venous blood ammonia
Inclusion period	February to August 2005
Notes	**Publication status:** full-paper article **Unpublished information:** requested but not received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Low risk	Blinded administration of interventions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment using placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. All participants included in analysis
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	High risk	Brookes Pharmaceutical Company provided study medication (Hepamerz)

Ahmad 2008 *(Continued)*

Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Alvares-da-Silva 2014

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal hepatic encephalopathy (n = 63) **Mean age ± SD:** L-ornithine L-aspartate 51.3 ± 13.5 years; placebo 52.5 ± 11.5 years **Proportion of men:** L-ornithine L-aspartate 54%; placebo 49% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 5 g of total dissolved solids **Control:** oral placebo (fructose 71.761 g/100 g, citrate 11 g, sodium citrate 10 g, mannitol 1.4, povidone 0.5 g, sodium cyclamate 0.81 g, saccharine 0.1 g, orange flavour 4 g, lemon flavour 0.4 g, sunset yellow 0.01 g) **Duration of treatment:** 60 days **Cointervention** lactulose (33%)
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (improvement defined as normalisation of neuropsychiatric tests), blood ammonia, serious adverse events, non-serious adverse events, quality of life at end of 60 days
Country	Brazil
Neuropsychiatric assessment	• Number Connection Tests-A and -B • Digital Symbol Test • Mini Mental State Examination (MMSE) • Critical Flicker Frequency • Electroencephalogram (every third participant only) • Arterial blood ammonia
Inclusion period	December 2009 to December 2010
Notes	**Protocol amendment:** investigators initially excluded people taking lactulose. Following new evidence (Bass 2010), investigators relaxed the criterion and included participants taking lactulose. **Previous overt hepatic encephalopathy:** in total, 17.5% of included participants had previous overt hepatic encephalopathy. **Publication status:** full-paper article **Unpublished information:** data on mean change in arterial ammonia concentrations taken from a presentation of a review of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017.
Risk of bias	

Alvares-da-Silva 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Serially numbered, opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment using placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. None of the participants excluded from reported analyses.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported in paper and trial protocol
For-profit funding	Low risk	No for-profit funding or other support (received financial support from an Incentive Fund for Research and Events)
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	Low risk	Low risk of bias
Overall bias assessment (non-mortality outcomes)	Low risk	Low risk of bias

Bai 2014

Methods	Single-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and no evidence of hepatic encephalopathy (n = 40). Participants were allocated after undergoing insertion of a transjugular intrahepatic portosystemic shunt **Mean age ± SD:** L-ornithine L-aspartate 49.7 ± 10.1 years; placebo 45.4 ± 9.6 years **Proportion of men:** 85% **Aetiology of cirrhosis:** alcohol (not reported); hepatitis B/C 83%
Interventions	**L-ornithine L-aspartate:** intravenous infusion 30 g/day **Control**: intravenous infusion of placebo (glucose) **Duration of treatment:** 7 days **Cointerventions:** lactulose, branched chain amino acids

Bai 2014 *(Continued)*

Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (number who developed an acute episode), blood ammonia, serious adverse events, non-serious adverse events assessed after 7 days
Country	China
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Number Connection Test-A • Serial Dotting Test • Line Tracing Test • Fasting and postprandial venous blood ammonia
Inclusion period	November 2011 to June 2012
Notes	**Publication status:** full-paper article **Unpublished information:** unpublished information from the authors sent by email in November 2015

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomised numbers
Allocation concealment (selection bias)	Low risk	Online central randomisation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial with no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes, and all participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported in paper and registered trial protocol
For-profit funding	Low risk	No funding or other support from for-profit company
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	Low risk	Low risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Blanco Vela 2011c

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and acute (overt) hepatic encephalopathy (n = 31) **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion 20 g/day and placebo enemata **Control:** lactulose enemata and intravenous infusion of placebo (not specified) **Duration of treatment:** 3 days **Cointerventions:** none
Outcomes	**Outcomes included in meta-analyses:** mortality, venous blood ammonia
Country	Mexico
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Glasgow Coma Scale • Clinical Hepatic Encephalopathy Staging Scale (CHESS) • Asterixis • Number Connection Test-A • Plasma ammonia • Portal Systemic Encephalopathy Score & Index
Inclusion period	November 2009 to June 2011
Notes	**Hepatic encephalopathy:** investigators evaluated hepatic encephalopathy based on overall scores and not number of participants with (or without) an overall improvement. Therefore, we were unable to include the trial in our analyses of hepatic encephalopathy. **Publication status:** abstract **Unpublished information:** received from authors via email in February and May 2016

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers (block randomisation)
Allocation concealment (selection bias)	Low risk	Online randomisation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial with no blinding of participants or personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment

Blanco Vela 2011c *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes. All participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported in abstract and trial registration
For-profit funding	Low risk	No funding or other support from for-profit company
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	Low risk	Low risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Chen 2005

Methods	Open, parallel-arm, single-centre, randomised clinical trial
Participants	**Included participants:** cirrhosis and acute, overt hepatic encephalopathy (n = 85) **Mean age ± SD:** L-ornithine L-aspartate 48.3 ± 11.7 years; control 47.8 ± 10.2 years **Proportion of men:** L-ornithine L-aspartate 67%; control 68% **Aetiology of cirrhosis:** alcohol 14%; hepatitis B/C 84%
Interventions	**L-ornithine L-aspartate:** intravenous infusion 40 g/day **Control:** no intervention **Duration of treatment:** 3 days **Cointervention:** none described
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (improvement defined as grade 0 on West Haven Scale), blood ammonia, serious and non-serious adverse events
Country	China
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Blood ammonia
Inclusion period	Unspecified
Notes	**Publication status:** full-paper article **Unpublished information from authors:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement

Chen 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial without blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial without blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. All participants included in analysis
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	Unclear risk	Not specified
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Feher 1997

Methods	Double-blind, parallel-arm, multicentre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis, hyperammonaemia but no evidence of overt hepatic encephalopathy (n = 80) **Mean age ± SD:** L-ornithine L-aspartate 50.0 ± 9.6 years; placebo 49.7 ± 12.9 years **Proportion of men:** 70% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion 40 g/day (2 participants) or 20 g/day (remaining participants) **Control:** intravenous infusion of placebo (isotonic saline) **Duration of treatment:** 7 days **Cointervention:** none reported
Outcomes	**Outcomes included in meta-analyses:** mortality, serious adverse events, non-serious adverse events, venous ammonia, assessed after a maximum of 7 days

Feher 1997 *(Continued)*

Country	Germany and Hungary
Neuropsychiatric assessment	• Mental status (blinded assessment of clinical status by physician) • Number Connection Test-A • Fasting and postprandial venous blood ammonia
Inclusion period	Before 1997
Notes	**Hepatic encephalopathy:** investigators did not look at changes in mental status as an outcome and as such we were unable to include this trial in our analyses of hepatic encephalopathy. **Publication status:** full-paper article **Unpublished information:** trial data also included in an unpublished meta-analysis from Merz contained in an internal report (trial label in the meta-analysis MRZ 9004-9003)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Blinded administration of intervention or placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors using placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data and all participants included in analysis
Selective reporting (reporting bias)	High risk	According to the unpublished meta-analysis by Merz, number connection test time was used as an efficacy parameter, but this was not reported in the published article.
For-profit funding	High risk	Funded by Merz
Other bias	Low risk	No additional biases identified
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Fleig 1999

Methods	Double-blind, parallel-arm, multicentre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal hepatic encephalopathy (n = 120), overt hepatic encephalopathy (n = 96), or no evidence of hepatic encephalopathy (n = 1) **Mean age ± SD:** L-ornithine L-aspartate 53.9 ± 12.4 years; placebo 52.3 ± 13.3 years **Proportion of men:** 72% **Aetiology of cirrhosis:** alcohol 79%; hepatitis B/C 16%
Interventions	**L-ornithine L-aspartate:** intravenous infusion 20 g/day **Control:** intravenous infusion of placebo (isotonic saline) **Duration of treatment:** 7 days **Cointervention:** none reported
Outcomes	**Outcomes included in meta-analyses:** none
Country	Germany
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Number Connection Tests-A and -B • Digit Symbol Test • Line Tracing Test • Serial Dotting Test • Psychometric Hepatic Encephalopathy Score (PHES)
Inclusion period	1998
Notes	**Publication status:** results published in abstract form (Fleig 1999); some additional trial data available in a published paper detailing the performance of psychometric tests used in evaluation of trial participants (Kircheis 2007) **Unpublished information:** published abstract did not provide information about clinical outcomes; we contacted the authors and the pharmaceutical company Merz, who sponsored the trial, requesting information about the included participants, methods, and outcomes; we received a reply explaining that data were not available for external distribution.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Blinded administration of interventions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessors using placebo

Fleig 1999 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Trial originally included 217 participants. In total, 216 received at least 1 dose of intervention. Outcome data only available for 192 participants. Remaining participants excluded from analyses. Reasons for losses to follow-up/withdrawals not described
Selective reporting (reporting bias)	High risk	Trial did not describe mortality.
For-profit funding	High risk	Sponsored by Merz
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Hasan 2012

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal or overt hepatic encephalopathy (n = 31). Trial did not describe number of participants with minimal/overt hepatic encephalopathy **Participant characteristics:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Control:** oral placebo (not specified) **Duration of treatment:** 7 days **Cointerventions:** none reported
Outcomes	**Outcomes included in meta-analyses:** none
Country	Indonesia
Neuropsychiatric assessment	• Mental status • Critical Flicker Frequency • Blood ammonia
Inclusion period	Not reported
Notes	**Publication status:** abstract **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement

Hasan 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Blinded administration of interventions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors using placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract did not describe missing outcome data
Selective reporting (reporting bias)	High risk	Abstract did not describe mortality
For-profit funding	Unclear risk	Not described
Other bias	Low risk	No additional biases
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Higuera-de la Tijera 2017

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, 3-way comparison, randomised clinical trial
Participants	**Included participants:** cirrhosis, variceal bleed, and no evidence of hepatic encephalopathy (n = 87) **Mean age ± SD:** L-ornithine L-aspartate 54.3 ± 7.7 years; lactulose 50.1 ± 11.3 years; rifaximin 53.0 ± 10.9; placebo 49.3 ± 9.5 years **Proportion of men:** 63% **Aetiology of cirrhosis:** alcohol 44.8%; hepatitis C 19.5%; other 35.6%
Interventions	**L-ornithine L-aspartate:** intravenous infusion 10 g/day **Lactulose:** oral lactulose 90 mL/day until melena resolved, then adjusted to dose-response **Rifaximin:** oral rifaximin 1.2 g/day **Placebo:** intravenous infusion saline solution 500 mL/day as placebo for L-ornithine L-aspartate; oral dextrose solution 90 mL/day as placebo for lactulose; oral dextrose tablets as placebo for rifaximin *each active participant group received 1 active preparation and 2 placebo preparations except for those in the placebo group who received 3 placebo preparations

Higuera-de la Tijera 2017 *(Continued)*

	Duration of treatment: 7 days, follow-up extended to 28 days **Cointervention:** treatment of acute variceal bleeding with haemodynamic stabilisation and vasopressors (octreotide or terlipressin) following the AASLD practice recommendations; oesophageal band ligation and sclerotherapy performed after endoscopic examination 12 hours postadmission for prevention of acute bleed from oesophageal varices and gastric varices; quinolones or cephalosporins were administered for 7 days for primary prophylaxis against infections except in the rifaximin arm where rifaximin was the only antibiotic administered.
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (number of participants who developed overt hepatic encephalopathy based on the West Haven Criteria), serious adverse events, non-serious adverse events assessed after 28 days
Country	Mexico
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Psychometric Hepatic Encephalopathy Score (PHES) • Critical Flicker Fusion Frequency
Inclusion period	July 2014 to June 2016
Notes	**Publication status:** abstract; full paper submitted for publication **Unpublished information:** data presented at the European Association for the Study of the Liver meeting Amsterdam April 2017; additional unpublished data received via email correspondence (May 2017)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated according to authors
Allocation concealment (selection bias)	Low risk	Interventions administered with blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded using placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data and all participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	High risk	Merz Pharma; Senosiain and Alfa Wassermann provided trial drugs but no additional sponsorship
Other bias	Low risk	No additional bias

Higuera-de la Tijera 2017 *(Continued)*

Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Hong 2003

Methods	Open, parallel-arm, single-centre, randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal hepatic encephalopathy (n = 39) **Mean age ± SD:** L-ornithine L-aspartate 43.1 ± 1.9 years; control 45.3 ± 3.5 years **Proportion of men:** 77% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 10 g/day **Control:** no intervention **Duration of treatment:** 3 days **Cointervention:** vitamins (type not specified) and hypoxanthosine
Outcomes	**Outcomes included in meta-analyses:** mortality, serious adverse effects, non-serious adverse effects, blood ammonia
Country	China
Neuropsychiatric assessment	• Number Connection Test • Critical Flicker Frequency • Blood ammonia
Inclusion period	June 2002 to November 2002
Notes	**Hepatic encephalopathy:** authors defined and reported change in mental status as group means of number connection test; we were unable to include this trial in our analysis of hepatic encephalopathy. **Publication status:** full-paper article **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	No blinding of participants or personnel

Hong 2003 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data and all participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	Unclear risk	Not described
Other bias	Low risk	No additional biases
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Kircheis 1997

Methods	Double-blind, parallel-arm, multicentre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal (n = 53) or chronic (n = 73) hepatic encephalopathy **Mean age ± SD:** L-ornithine L-aspartate 53.9 ± 12.4 years; placebo 52.3 ± 13.3 years **Proportion of men:** 72% **Aetiology of cirrhosis:** alcohol 79%; hepatitis B/C 16%
Interventions	**L-ornithine L-aspartate:** intravenous 20 g/day **Control:** intravenous riboflavin and polyethylene glycol (placebo) **Duration of treatment:** 7 days **Cointerventions:** none
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (improvement defined as mental state grade based on the West Haven Criteria or Number Connection Test-A results, or both), serious adverse events, non-serious adverse events, blood ammonia assessed after a maximum of 7 days
Country	Germany
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Asterixis • Number Connection Test-A • Fasting and postprandial venous blood ammonia • Portal Systemic Encephalopathy Sum & Index
Inclusion period	April 1990 to May 1991

Kircheis 1997 *(Continued)*

Notes	**Publication status:** full-paper article **Unpublished information:** trial also described in an unpublished meta-analysis from Merz available in an internal report (trial label in the meta-analysis MRZ 9004-8908)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Low risk	Blinded administration of coded drug containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors using placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data for clinical outcomes and all participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	High risk	Sponsored by Merz; company staff involved in trial
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Maldonado 2010

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal hepatic encephalopathy (n = 22) **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral (dose not described) **Control:** oral placebo (not specified)

Maldonado 2010 *(Continued)*

	Duration: 7 days **Cointerventions**: none reported
Outcomes	**Outcomes included in meta-analyses:** none
Country	Mexico
Neuropsychiatric assessment	• Blood ammonia at baseline and 60 minutes after a 10g post-glutamine load
Inclusion period	Not described
Notes	**Publication status:** abstract **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment using placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	Trial did not describe effect of intervention on minimal hepatic encephalopathy.
For-profit funding	Unclear risk	Not described
Other bias	Low risk	No other biases
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1987

Methods	Double-blind, placebo-controlled, randomised clinical trial

Merz 1987 *(Continued)*

Participants	**Included participants:** cirrhosis with minimal or overt hepatic encephalopathy (n = 10) **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Control:** placebo (not specified) **Duration:** 14 days **Cointerventions**: not described
Outcomes	**Outcomes included in meta-analyses:** hepatic encephalopathy, blood ammonia
Country	Not available
Neuropsychiatric assessment	• Hepatic encephalopathy grade • Number Connection Test • Blood ammonia
Inclusion period	1989 to 1991
Notes	**Publication status:** unpublished **Unpublished information:** some data available from a presentation of a review of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published data unavailable
Allocation concealment (selection bias)	Unclear risk	Published data unavailable
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Published data unavailable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Published data unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz

Merz 1987 *(Continued)*

Other bias	High risk	Unpublished trial, non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1988a

Methods	Double-blind, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal or overt hepatic encephalopathy (n = 42). Number of participants with minimal and overt hepatic encephalopathy not described **Mean age** ± **SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Control:** placebo (not specified) **Duration:** 31 days **Cointerventions**: not reported
Outcomes	**Outcomes included in meta-analyses:** hepatic encephalopathy
Country	Not described
Neuropsychiatric assessment	• Hepatic encephalopathy grade • Number Connection Test • Blood ammonia
Inclusion period	1989 to 1991
Notes	**Publication status:** unpublished **Unpublished information:** some data available from a presentation of a review of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published data unavailable
Allocation concealment (selection bias)	Unclear risk	Published data unavailable
Blinding of participants and personnel (performance bias)	Unclear risk	Published data unavailable

Merz 1988a *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Published data unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished trial; non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1988b

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal or overt hepatic encephalopathy, hyperammonaemia, and recent bleeding from oesophageal varices (planned n = 38; evaluable data in 8) **Mean age ± SD:** L-ornithine L-aspartate 62.8 ± 2.9 years; placebo 51.3 ± 11.5 years **Proportion of men:** approximately 70% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion 40 g/day **Control:** intravenous infusion placebo (isotonic saline) **Duration of treatment:** 7 days **Cointervention:** none reported
Outcomes	**Outcomes included in meta-analyses:** hepatic encephalopathy, hepatic encephalopathy, blood ammonia, non-serious adverse events
Country	Germany (Bonn)
Neuropsychiatric assessment	• Mental status (Holms grade) • Number Connection Test-A • Fasting and postprandial venous blood ammonia and postprandial arterial blood ammonia
Inclusion period	1988 to 1989
Notes	**Publication status:** unpublished

Merz 1988b *(Continued)*

Unpublished information: some data included in a meta-analysis published in an abstract presented at the AASLD (Delcker 2000a); further details obtained from an internal unpublished Merz report which stated that it was planned to include 38 participants but only 8 were evaluable (Delcker 2000b); for purposes of this review, we assumed that only 8 participants were enrolled; some data on outcomes were also available from a presentation of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded using placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished, non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1988c

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal or overt hepatic encephalopathy and hyperammonaemia (planned n = 42; evaluable n = 11). Number of participants with minimal and overt hepatic encephalopathy not described **Mean age ± SD**: L-ornithine L-aspartate 59.2 ± 9.2 years; control 50.0 ± 14.1 years **Proportion of men:** approximately 70% **Aetiology of cirrhosis:** not reported

Merz 1988c *(Continued)*

Interventions	**L-ornithine L-aspartate:** intravenous infusion 40 g/day (2 participants) or 20 g/day (remaining participants) **Control:** intravenous infusion placebo (glucose) **Duration of treatment:** 7 days **Cointerventions:** none reported
Outcomes	**Outcomes included in meta-analyses:** hepatic encephalopathy, blood ammonia, non-serious adverse events
Country	Germany (GroB-Gerau)
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Number Connection Test A • Postprandial venous blood ammonia
Inclusion period	1989 to 1992
Notes	**Publication status:** unpublished **Unpublished information:** some data included in a meta-analysis published as an abstract presented at the AASLD (Delcker 2000a). Further details obtained from an internal unpublished Merz report which stated that it was planned to include 38 participants but only 11 were evaluable (Delcker 2000b); for purposes of this review we assumed that only 11 participants were enrolled; some data on outcomes were available from a presentation of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors using placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished, non-peer-reviewed data

Merz 1988c *(Continued)*

Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1988d

Methods	Double-blind, cross-over, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and hepatic encephalopathy; number unknown **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion (dose not specified) **Control:** intravenous infusion of placebo (not specified) **Duration of treatment:** 1 day **Cointervention:** none reported
Outcomes	**Outcomes included in meta-analyses:** none
Country	Unknown
Neuropsychiatric assessment	Not reported
Inclusion period	Pre-1999
Notes	**Publication status:** unpublished **Unpublished information:** trial identified in an internal unpublished Merz report as 1 of 6 trials excluded from their meta-analysis because duration of treatment did not match requirements for inclusion of 7 days (Delcker 2000b); additional information on this trial was available from a presentation of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded using placebo

Merz 1988d *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded using placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished, non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1989a

Methods	Double- blind, parallel-arm, multicentre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal or overt hepatic encephalopathy and hyperammonaemia (planned n = 66; evaluable n = 21). Number of participants with minimal or overt hepatic encephalopathy not reported **Mean age ± SD:** L-ornithine L-aspartate 52.6 ± 10.2 years; placebo 57.2 ± 11.9 years **Proportion of men:** approximately 70% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion 40 g/day **Control:** intravenous infusion placebo (isotonic saline) **Duration of treatment:** 7 days **Cointervention:** none reported
Outcomes	**Outcomes included in meta-analyses:** hepatic encephalopathy, blood ammonia, non-serious adverse events
Country	Germany
Neuropsychiatric assessment	• Mental status (Holm grade) • Number Connection Test-A • Fasting and postprandial venous blood ammonia
Inclusion period	1989 to 1990
Notes	**Publication status:** unpublished

Merz 1989a *(Continued)*

Unpublished information: some data were included in a meta-analysis published as an abstract presented at the AASLD (Delcker 2000a). Further details obtained from an internal unpublished Merz report which stated that it was planned to include 66 participants but only 21 were evaluable (Delcker 2000b). For purposes of this review, we assumed that only 21 participants were enrolled. Some data on outcomes were available from a presentation of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors using placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished, non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1989b

Methods	Double-blind randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal or overt hepatic encephalopathy (n = 10). Number of participants with minimal or overt hepatic encephalopathy not reported **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day

Merz 1989b *(Continued)*

	Control: placebo (not specified) **Duration:** 14 days **Cointerventions**: not described
Outcomes	**Outcomes included in meta-analyses:** hepatic encephalopathy, blood ammonia
Country	Not available
Neuropsychiatric assessment	• Hepatic encephalopathy grade • Number Connection Test • Blood ammonia
Inclusion period	1989 to 1992
Notes	**Publication status:** unpublished **Unpublished information:** some data were available from a presentation of a review of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published data unavailable
Allocation concealment (selection bias)	Unclear risk	Published data unavailable
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Published data unavailable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Published data unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished trial; non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1992a

Methods	Unpublished, double-blind, placebo-controlled, parallel design, randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal or overt hepatic encephalopathy (n = 16). Number of participants with minimal and overt hepatic encephalopathy not described **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion 40 g/day **Control:** intravenous infusion of placebo **Duration of treatment:** 7 days **Cointervention:** none reported
Outcomes	**Outcomes included in meta-analyses:** hepatic encephalopathy; blood ammonia
Country	Germany
Neuropsychiatric assessment	• Mental state • Fasting blood ammonia
Inclusion period	1994 to 1995
Notes	Trial was 1 of a number considered by Merz for inclusion in a meta-analysis of intravenous L-ornithine L-aspartate detailed in an internal report (Delcker 2000b). Although trial was described as double-blind, placebo-controlled, parallel-design, randomised clinical trial, it was excluded from the meta-analysis because L-ornithine L-aspartate had been used for an indication other than hepatic encephalopathy; no other details provided. A trial with the same Merz ID number was included in a meta-analysis of published and unpublished trials in people with cirrhosis and hepatic encephalopathy presented at the ISHEN meeting in Delhi 2017 (Butterworth 2017). In this report, 16 participants with cirrhosis and minimal or overt hepatic encephalopathy were randomised to either L-ornithine L-aspartate 40 g/day, by intravenous infusion for 7 days, or to a placebo; benefit was observed in mental status and in fasting blood ammonia concentrations favouring L-ornithine L-aspartate.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published data unavailable
Allocation concealment (selection bias)	Unclear risk	Published data unavailable
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Published data unavailable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Published data unavailable

Merz 1992a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished trial; non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1994a

Methods	Double-blind, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal or overt hepatic encephalopathy (n = 73) **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Control:** not described **Duration:** unclear **Cointerventions**: not described
Outcomes	**Outcomes included in meta-analyses:** none
Country	Not described
Neuropsychiatric assessment	• Mental status • Number Connection Test • Blood ammonia
Inclusion period	1994 to 1997
Notes	**Publication status:** unpublished **Unpublished information:** limited data were available from a presentation of a review of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017)

Risk of bias

Bias	Authors' judgement	Support for judgement

Merz 1994a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Published data unavailable
Allocation concealment (selection bias)	Unclear risk	Published data unavailable
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Published data unavailable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Published data unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished trial; non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Merz 1994b

Methods	Double-blind, double-dummy, randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal or overt hepatic encephalopathy (n = 96). Number of participants with minimal or overt hepatic encephalopathy not reported **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion 60 g/day and 'lactulose' placebo (not specified) **Control:** oral lactulose and placebo infusion (not specified) **Duration:** 3 days **Cointerventions**: not described
Outcomes	**Outcomes included in meta-analysis:** none
Country	No information available

Merz 1994b *(Continued)*

Neuropsychiatric assessment	No information available
Inclusion period	1995 to 1999
Notes	**Publication status:** unpublished **Unpublished information:** trial was referred to in an internal Merz report as a double-blind, double-dummy randomised trial comparing L-ornithine L-aspartate versus a treatment alternative (lactulose) (Delcker 2000b); it was excluded from the Merz meta-analysis as it was not placebo controlled. Additional information was available from a presentation of unpublished Merz trials at the ISHEN meeting in Delhi 2017 where it was referred to as randomised but not blinded (Butterworth 2017).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published data unavailable
Allocation concealment (selection bias)	Unclear risk	Published data unavailable
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Published data unavailable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Published data unavailable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published data unavailable
Selective reporting (reporting bias)	Unclear risk	Published data unavailable
For-profit funding	High risk	Sponsored by Merz
Other bias	High risk	Unpublished trial; non-peer-reviewed data
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Mittal 2011

Methods	Open, parallel-arm, single-centre, 4-way comparison, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal hepatic encephalopathy (n = 160)

Mittal 2011 *(Continued)*

	Mean age ± SD: L-ornithine L-aspartate 42.2 ± 8.7 years; control (no intervention) 41.2 ± 11.9 years; lactulose 43.9 ± 10.9 years; probiotics 44.3 ± 11.8 years **Proportion of men:** 77% **Aetiology of cirrhosis:** alcohol 41%; hepatitis B/C 34%
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Comparative groups:** no intervention; lactulose 30-60 mL adjusted based on stool frequency; probiotic 100 billion units twice daily **Duration:** 3 months **Cointerventions:** salt restricted diet (< 2 g sodium/day); investigators encouraged supplementation with a casein-based protein, 1 g/kg/day
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (normalisation of psychometric tests), serious adverse events, non-serious adverse events, blood ammonia
Country	India
Neuropsychiatric assessment	• Mental status (West Haven criteria) • Number Connection Tests-A and -B • Figure Connection Tests-A, and -B • Arterial blood ammonia
Inclusion period	October 2007 to October 2009
Notes	**Publication status:** full-paper article **Unpublished information:** additional information about methods used to allocate participants provided by author (V Mittel: personal communication)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Low risk	Central independent unit
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of participants or personnel
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data for any clinical outcome measure and all participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported

Mittal 2011 *(Continued)*

For-profit funding	Low risk	No external funding
Other bias	Low risk	No other biases
Overall bias assessment (mortality)	Low risk	Low risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Ndraha 2011

Methods	Open, parallel-arm, multicentre, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal hepatic encephalopathy (n = 34) **Mean age ± SD:** L-ornithine L-aspartate 53.2 ± 11.8 years; control 51.8 ± 10.6 years **Proportion of men:** 91% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Control:** no intervention **Duration:** 14 days **Cointerventions:** branched chain amino acids (1.2 g protein/kg/day to 1.5 g protein/kg/day)
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (prevention of clinically overt hepatic encephalopathy), serious adverse events, non-serious adverse events assessed after 14 days
Country	Indonesia
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Plasma ammonia • Critical Flicker Frequency
Inclusion period	June to October 2009
Notes	**Publication status:** full-paper **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Ndraha 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants with missing outcome data not described
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	Unclear risk	Not described
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Nimanong 2010

Methods	Double- blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and acute (overt) hepatic encephalopathy, Grade II or III according to West Haven Criteria (n = 35) **Mean age ± SD:** not reported **Proportion of men:** not reported **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Control:** oral placebo (not specified) **Duration:** 7 days **Cointerventions:** none reported
Outcomes	**Outcomes included in meta-analyses:** mortality and serious adverse events assessed after 7 days
Country	Thailand
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Asterixis • Number Connection Test • Electroencephalogram • Plasma ammonia

Nimanong 2010 *(Continued)*

	• Portal Systemic Encephalopathy Sum & Index
Inclusion period	Not described
Notes	**Hepatic encephalopathy:** data on the number of participants with improvement in their mental status were unavailable; we were unable to include this trial in our analyses of hepatic encephalopathy. **Publication status:** abstract **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described; possibly low risk of bias (stratified allocation based on creatinine)
Allocation concealment (selection bias)	Low risk	Blinded administration of interventions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel with placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessors with placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up not described
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes reported in abstract and electronic trial registration
For-profit funding	Low risk	None
Other bias	Low risk	No additional biases identified
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Oruc 2010

Methods	Open, parallel-arm, single-centre, placebo-controlled randomised clinical trial
Participants	**Included participants:** cirrhosis and acute, (overt) hepatic encephalopathy admitted to an intensive care unit (n = 47) **Mean age** ± **SD:** not described **Proportion of men:** not described

Oruc 2010 *(Continued)*

	Aetiology of cirrhosis: not described
Interventions	**L-ornithine L-aspartate:** intravenous infusion 40 g/day **Control:** intravenous infusion of placebo (isotonic saline) **Duration:** 5 days **Cointerventions**: lactulose and antibiotics
Outcomes	**Outcomes included in meta-analyses:** none
Country	Turkey
Neuropsychiatric assessment	• Mental status (West Haven criteria) • Fasting plasma ammonia • Critical Flicker Frequency
Inclusion period	Not described
Notes	**Publication status:** abstract **Unpublished information:** requested but none received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial without blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial without blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data not described
Selective reporting (reporting bias)	High risk	Publication described proportion of participants who died and proportion without improved manifestations of hepatic encephalopathy, but it did not describe number of participants allocated to intervention and control groups.
For-profit funding	Unclear risk	Not described
Other bias	Low risk	No other bias identified
Overall bias assessment (mortality)	High risk	High risk of bias

Oruc 2010 *(Continued)*

Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Poo 2006

Methods	Open-label, parallel-arm, single-centre, randomised clinical trial
Participants	**Included participants:** cirrhosis and chronic hepatic encephalopathy (n = 20) **Mean age ± SD:** L-ornithine L-aspartate 60 ± 6 years; lactulose 64 ± 7 years **Proportion of men:** 10% **Aetiology of cirrhosis:** alcohol not reported; hepatitis B/C 45%
Interventions	**L-ornithine L-aspartate:** oral 9 g/day or 18 g/day (at the investigators discretion) **Control:** 30 mL to 60 mL lactulose **Duration:** 14 days **Cointerventions:** none described
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (improvement defined as reduction in grade on the West Haven Scale), serious adverse events, quality of life, blood ammonia assessed after maximum of 14 days
Country	Mexico
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Number Connection Test-A • Asterixis • Fasting venous plasma ammonia • Portal Systemic Encephalopathy Sum & Index
Inclusion period	May 2004 to February 2006
Notes	**Non-serious adverse events:** data on number of participants who reported non-serious adverse events were unavailable; we were unable to include this trial in our analyses of non-serious adverse events. **Publication status:** full-paper article **Unpublished information:** requested but none received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described

Poo 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes, and the analyses include all participants
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes are defined and reported
For-profit funding	High risk	Merz provided the L-ornithine L-aspartate
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Puri 2010

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal hepatic encephalopathy (n = 78) **Mean age ± SD:** 41.12 ± 9.43 years **Proportion of men:** 86% **Aetiology of cirrhosis:** not reported
Interventions	L-**ornithine L-aspartate:** oral (dose not reported) **Control:** placebo (not specified) **Duration:** 14 days **Cointerventions:** none reported
Outcomes	**Outcomes included in meta-analyses:** mortality, serious adverse events, blood ammonia assessed after 14 days
Country	India
Neuropsychiatric assessment	• Number Connection Test • Digit Symbol Test • Block Design Test • Blood ammonia • Cognitive evoked potential-P300

Puri 2010 *(Continued)*

	• Critical Flicker Frequency
Inclusion period	Not reported
Notes	**Hepatic encephalopathy:** number with (or without) overall improvement in hepatic encephalopathy not reported; we were unable to include this trial in our analyses of hepatic encephalopathy **Publication status:** abstract **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Blinded administration of interventions
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment using placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants who died or developed serious adverse events excluded from analyses of hepatic encephalopathy
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported. Hepatic encephalopathy assessed using psychometric tests without providing number with (or without) an overall improvement.
For-profit funding	Unclear risk	Not described
Other bias	Low risk	No other biases
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Schmid 2010

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled, randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal (n = 12) or chronic (n = 33) hepatic encephalopathy **Mean age ± SD:** L-ornithine L-aspartate 56.1 ± 9.1 years; control 54.0 ± 12.0 years **Proportion of men:** 66%

Schmid 2010 *(Continued)*

	Aetiology of cirrhosis: alcohol 56%; hepatitis B/C 17%
Interventions	**L-ornithine L-aspartate:** intravenous infusion 20 g/day **Control:** intravenous infusion of placebo (glucose) **Duration:** 8 days **Cointerventions:** none reported
Outcomes	**Outcomes included in meta-analyses:** non-serious adverse events; blood ammonia assessed after 8 days
Country	Austria
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Number Connection Tests-A and -B • Digit Symbol Test • Line Tracing Test • Serial Dotting Test • Arterial blood ammonia • Portal Systemic Encephalopathy Sum & Index • Critical Flicker Frequency
Inclusion period	March 2003 to July 2006
Notes	**Publication status:** full-paper article **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Blinded administration of coded containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded using placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	Authors specifically stated that they excluded participants from their analyses. Number of participants with missing outcome data described, but allocation of those participants was not. Therefore. we were unable to include the data in worst-case scenario analyses.
Selective reporting (reporting bias)	High risk	Mortality not described. Allocation group of participants who experienced a serious adverse event not described. Trial described hepatic encephalopathy based on psychometric test results without providing information about the number of participants with (or without) improved manifestations

Schmid 2010 *(Continued)*

For-profit funding	Unclear risk	Not described
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Sharma 2014

Methods	Open, parallel-arm, single-centre, placebo-controlled 4-way randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal hepatic encephalopathy (n = 124) **Mean age ± SD:** L-ornithine L-aspartate 42.0 ± 11.4 years; control 38.0 ± 11.8 years; rifaximin 43.9 ± 12.5 years; probiotics 33.9 ± 13.2 years **Proportion of men:** 38% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Placebo:** placebo capsule (not specified), 2 capsules/day **Rifaximin:** 1200 mg/day **Probiotic:** Cap Velgut, 1 capsule/day; *each patient group only received their corresponding treatment preparation with no dummy treatments **Duration:** 2 months **Cointerventions:** investigators encouraged participants to supplement with casein-based protein, approximately 1 g/kg/day
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (improvement defined as a score < 2 SDs from the mean score of psychometric tests) assessed after 2 months
Country	India
Neuropsychiatric assessment	• Clinical hepatic encephalopathy staging scale • Number Connection Test-A • Figure Connection Test-A • Digital SymbolTest • Critical Flicker Frequency
Inclusion period	August 2009 to August 2010
Notes	**Serious adverse events:** while the total number of participants who developed overt hepatic encephalopathy was reported, it was unclear how many participants from each treatment arm did so; therefore, we were unable to include this trial in our analyses of serious adverse events. **Publication status:** full-paper article **Unpublished information:** requested but none received

Sharma 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with random generator
Allocation concealment (selection bias)	Low risk	Central independent unit
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up clearly described, and all participants included in analyses using last observation carry forward (binary outcomes) or median values (for continuous outcomes)
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	Low risk	No external funding
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	Low risk	Low risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Sidhu 2018

Methods	Double-blind, parallel-arm, multicentre, placebo-controlled randomised clinical trial
Participants	**Included participants:** cirrhosis and acute (overt) hepatic encephalopathy West Haven Grade II to IV (n = 193) **Mean age ± SD:** L-ornithine L-aspartate 49.6 ± 10.5 years; placebo 48.9 ± 12.7 years **Proportion of men:** L-ornithine L-aspartate 90.8%; placebo 85.7% **Aetiology of cirrhosis:** alcohol 18%; hepatitis B/C 34%; alcohol and hepatitis B/C 37%; other 10%
Interventions	**L-ornithine L-aspartate:** intravenous infusion 30 g/day **Control:** placebo intravenous infusion (sterile water and 5% dextrose) **Duration:** 5 days **Cointerventions:** all participants received lactulose and 1 participant in the placebo group received branched-chain amino acids

Sidhu 2018 *(Continued)*

Outcomes	**Outcomes included in meta-analyses:** mortality after 4 weeks; hepatic encephalopathy (resolution defined as disappearance of overt hepatic encephalopathy; improvement defined as decrease in hepatic encephalopathy by 1 Grade or more but not reaching covert hepatic encephalopathy); blood ammonia; serious adverse events; non-serious adverse events assessed after 5 days
Country	India
Neuropsychiatric assessment	• Mental status (Modified West Haven Criteria) • Venous blood ammonia
Inclusion period	December 2013 to January 2017
Notes	**Publication status:** full-paper article **Unpublished information:** additional unpublished information received from the authors via email in April 2017

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Electronic randomisation (www.sealedenvelope.com)
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded using placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	High risk	L-ornithine L-aspartate and placebo provided by Win-Medicare Pvt. Ltd. (India)
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Stauch 1998

Methods	Double-blind, parallel-arm, multicentre, placebo-controlled randomised clinical trial
Participants	**Included participants:** cirrhosis and minimal (n = 23) or chronic (n = 43) hepatic encephalopathy **Mean age ± SD:** L-ornithine L-aspartate 52.7 ± 10.6 years; placebo 54.1 ± 12.9 years **Proportion of men:** 64% **Aetiology of cirrhosis:** alcohol 82%; hepatitis B/C 13%
Interventions	**L-ornithine L-aspartate:** oral 18 g/day **Control:** oral placebo (fructose) **Duration:** 14 days **Cointerventions:** none described
Outcomes	**Outcomes included in meta-analyses:** mortality; hepatic encephalopathy (improvement defined based on the Number Connection Test-A results and West Haven Criteria) assessed after 14 days; blood ammonia; serious adverse events; non-serious adverse events
Country	Germany
Neuropsychiatric assessment	• Mental status (West Haven Criteria) • Number Connection Test-A • Fasting and postprandial venous blood ammonia • Portal Systemic Encephalopathy Sum & Index
Inclusion period	March 1989 to February 1990
Notes	**Blood ammonia concentrations:** data on blood ammonia concentrations for participants with minimal hepatic encephalopathy were available from the full-paper article; data on blood ammonia concentrations for participants with minimal or chronic overt hepatic encephalopathy were available from a presentation of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017, but not for all participants (n = 63). **Publication status:** full-paper article **Unpublished information:** data on blood ammonia concentrations were available from a presentation of published and unpublished Merz trials at the ISHEN meeting in Delhi 2017 (Butterworth 2017).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel blinded using placebo
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessors using placebo

Stauch 1998 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data and all participants included in analyses
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	High risk	Some investigators were affiliated with Merz
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Taylor-Robinson 2017

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled randomised clinical trial
Participants	**Included participants:** cirrhosis with minimal hepatic encephalopathy (n = 7) or no evidence of hepatic encephalopathy (n = 27) **Mean age ± SD:** L-ornithine L-aspartate 56.86 ± 6.7 years; placebo 55.25 ± 7.0 years **Proportion of men:** 68% **Aetiology of cirrhosis:** alcohol 47%; hepatitis C 35%; other 18%
Interventions	**L-ornithine L-aspartate:** 14 participants received oral 18 g/day **Control:** 20 received identically packaged placebo (not specified) **Duration:** 12 weeks **Cointerventions:** none described apart from individual concurrent medication
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (change in psychometric test performance), serious adverse effects, non-serious adverse effects assessed after 12 weeks
Country	UK
Neuropsychiatric assessment	• Mental status • Serial Dotting Test • Line Tracing Test • Digit Symbol Test • Cogstate test battery • Stroop test • Wechsler test of adult reading
Inclusion period	August 2013 to June 2015
Notes	**Publication status:** abstract

Taylor-Robinson 2017 *(Continued)*

Unpublished information: unpublished information received from authors via email in March 2017

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation at source
Allocation concealment (selection bias)	Low risk	Central randomisation at source and concealed using sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of personnel. Partially unblinded after completion for statistical analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes, and analyses include all participants
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	High risk	Investigator funded by grant from Merz Pharmaceuticals GmbH, Frankfurt, Germany
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Varakanahalli 2017

Methods	Double-blind, parallel-arm, single-centre, placebo-controlled randomised clinical trial
Participants	**Included participants:** cirrhosis with a recent acute episode of overt hepatic encephalopathy now recovered (n = 150) **Mean age ± SD:** not specified **Proportion of men:** not specified **Aetiology of cirrhosis:** not specified
Interventions	**L-ornithine L-aspartate:** oral 18 g/day (n = 73) **Control:** placebo, similar amount of identically packaged placebo (n = 72) **Duration:** 6 months

Varakanahalli 2017 *(Continued)*

	Cointerventions: none described apart from individual concurrent medication
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy, blood ammonia, quality of life
Country	India
Neuropsychiatric assessment	• Mental status • Number Connection Test • Figure Connection Test • Digit Symbol Test • Serial Dotting Test • Line Tracing Test • Critical Flicker Frequency • Arterial ammonia
Inclusion period	Not specified
Notes	**Publication status:** abstract **Unpublished information:** requested but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based random number generator
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	Unclear risk	Not specified
Other bias	Low risk	Low risk of bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

Zhou 2013

Methods	Open, parallel-arm, single-centre, randomised clinical trial
Participants	**Included participants:** cirrhosis and acute (overt) hepatic encephalopathy (n = 84) **Mean age ± SD:** L-ornithine L-aspartate 47.6 ± 10.5 years; control 48.2 ± 11.3 years **Proportion of men:** 57.1% **Aetiology of cirrhosis:** not reported
Interventions	**L-ornithine L-aspartate:** intravenous infusion 10 to 15 g/day **Duration:** 7 to 14 days **Cointerventions:** naloxone 3 mg
Outcomes	**Outcomes included in meta-analyses:** mortality, hepatic encephalopathy (based on the clinical assessments), serious adverse events, blood ammonia assessed after a maximum of 14 days
Country	China
Neuropsychiatric assessment	• Hasegawa's Dementia Scale • Mini Mental State Examination (MMSE) • Portal Systemic Encephalopathy Sum & Index • Magnetic resonance imaging
Inclusion period	March 2007 to May 2009
Notes	**Publication status:** full-paper article **Unpublished information:** requested but none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up excluded from analyses

Zhou 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported
For-profit funding	Unclear risk	Funding not described
Other bias	Low risk	No other bias
Overall bias assessment (mortality)	High risk	High risk of bias
Overall bias assessment (non-mortality outcomes)	High risk	High risk of bias

AASLD: American Association for the Study of Liver Diseases; ISHEN: International Society for Hepatic Encephalopathy and Nitrogen Metabolism; n: number of participants; PHES: Psychometric Hepatic Encephalopathy Score; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdo-Francis 2010	Observational retrospective study evaluating duration of hospital stay in 80 participants with acute (overt) hepatic encephalopathy treated with L-ornithine L-aspartate or lactulose. L-ornithine L-aspartate was associated with a shorter length of stay and a shorter time to recovery.
Acharya 2009	Double-blind, parallel-arm, randomised clinical trial comparing intravenous L-ornithine L-aspartate 30 g/day versus placebo involving 201 participants with acute liver failure; none had cirrhosis. Duration of treatment 3 days. No differences between allocation groups in mortality, hepatic encephalopathy, or blood ammonia.
Aidrus 2015	Placebo-controlled, open, parallel-arm, quasi-randomised trial. No participants died and none experienced adverse events 102 participants with cirrhosis and acute, overt (grade II to IV) hepatic encephalopathy. 2 participants were discharged or referred before data collection and were therefore excluded from analyses. **Mean age ± SD:** L-ornithine L-aspartate 49.7 ± 12.3 years; placebo 46.0 ± 9.8 years **Proportion of men:** L-ornithine L-aspartate 60%; placebo 56% **Aetiology of cirrhosis:** hepatitis B/C 100% **Interventions:** L-ornithine L-aspartate**:** intravenous 10 g/day; placebo (intravenous saline) **Duration of treatment:** 3 days **Cointerventions:** lactulose and metronidazole **Outcomes assessed:** mortality, hepatic encephalopathy (improvement defined as West Haven Grade 0), blood ammonia assessed after 3 days **Country:** Pakistan **Mental status:** West Haven Criteria **Ammonia:** plasma ammonia **Inclusion period:** July 2013 to June 2014 **Publication status:** full-paper article

Study	Reason for exclusion
	Unpublished information: we received information about the methods used to allocate participants from Dr Salma Razzaque on 9 May 2016. This was described as "convenience sampling," which consisted of allocation based on the hospital admission number. Investigators administered the intervention to people with even numbers and the placebo to people with uneven numbers.
Badea 2015	Case-series of people with cirrhosis and acute variceal bleeding given either lactulose (n = 52) or lactulose and L-ornithine L-aspartate (n = 52) for primary prevention of hepatic encephalopathy. Publication reported that the combination of lactulose and L-ornithine L-aspartate was more effective than lactulose alone.
Delcker 2002	Observational study evaluating the acute effect of intravenous L-ornithine-L-aspartate 40 g on cerebral magnetic resonance spectroscopy in 15 participants with chronic stable hepatic encephalopathy. Changes were found in the cerebral glutamate + glutamine/creatine ratios which were associated with arterial ammonia concentrations.
Grover 2017	Mechanistic non-randomised, open-label intervention study assessing the efficacy of magnetisation transfer and diffusion-weighted magnetic resonance imaging and magnetic resonance spectroscopy for detecting minimal hepatic encephalopathy in people with cirrhosis receiving oral L-ornithine L-aspartate for 28 days.
Lim 2010	Observational retrospective study including 12 participants with cirrhosis and chronic (overt) hepatic encephalopathy unresponsive to lactulose. Treatment with L-ornithine L-aspartate reduced number of readmissions to hospital after a median treatment duration of 7 months.
McPhail 2013	Observational study evaluating 4 weeks of treatment with L-ornithine L-aspartate. Study included 22 participants with stable, biopsy-confirmed cirrhosis and previous minimal hepatic encephalopathy. Psychometric Hepatic Encephalopathy Score improved after treatment; improvement associated with changes in regional brain volume and basal ganglia in magnetic resonance spectroscopy.
Merz 1988e	Unpublished study identified in a Merz-sponsored presentation at a meeting of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) in Delhi 2017 (Butterworth 2017). Study involved 45 participants with cirrhosis and minimal or overt hepatic encephalopathy given L-ornithine L-aspartate 27 g for 14 days but was excluded from the performed meta-analysis as it was not randomised or blinded; unclear whether it was controlled.
Merz 1991	Unpublished study identified in an internal Merz report (Delcker 2000b). Excluded from their internal meta-analysis as it was not randomised or controlled.
Merz 1992b	Unpublished study identified in an internal Merz report (Delcker 2000b). Excluded from their internal meta-analysis as it was not randomised or controlled.
Müting 1980	Observational study evaluating the acute effects of L-ornithine L-aspartate on hepatic encephalopathy in 10 participants with cirrhosis with or without surgically created portosystemic shunts.
Ndhara 2010	Open, single-centre, observational study including 17 participants with cirrhosis and minimal hepatic encephalopathy treated with oral L-ornithine L-aspartate 18 g/day combined with a diet of branched chain amino acids and protein. Based on an assessment of mental status using the critical flicker frequency, study found that intervention had a beneficial effect on hepatic encephalopathy.
Ong 2011	Open, multicentre, outpatient, observational study evaluating the effect of oral L-ornithine L-aspartate 18 g/day in participants with overt hepatic encephalopathy. Study found improvements in health-related quality of life assessed using the Chronic Liver Disease Questionnaire and in symptom severity.

Study	Reason for exclusion
Popa 2015	Case-series of people with cirrhosis and minimal hepatic encephalopathy treated with rifaximin or rifaximin + L-ornithine L-aspartate. Reported differences in blood test results, but did not describe serious adverse events.
Rees 2000	Descriptive trial including 8 participants with cirrhosis undergoing a transjugular intrahepatic shunt venogram. Participants kept their portal catheter for 24 hours to allow measurement of ammonia concentrations on 2 consecutive days. Underwent psychometric tests and electroencephalography before and after administration of oral glutamine 20 g following an infusion of a placebo or a single dose of L-ornithine L-aspartate. Sequence was randomised and infusions were administered in double-blind method. Results showed that infusion of L-ornithine L-aspartate had no effect on the outcomes assessed; there was no information on primary outcomes of interest in this review.
Reikowski 1982	Open, single-centre, case series including 3 participants with cirrhosis and acute (overt) hepatic encephalopathy treated with L-ornithine L-aspartate 9 g/day. Found a potential beneficial effect on plasma ammonia concentrations.
Staedt 1993	Descriptive study evaluating dose-dependent effects of ornithine aspartate on postprandial hyperammonaemia and plasma amino acids. Trial included 10 participants with cirrhosis allocated to 1 of 4 infusion series on separate days. Infusions were placebo (saline), or L-ornithine L-aspartate 5 g, 20 g, or 40 g (4-fold cross-over design). Trial designed as a dose finding study and not a clinical trial.
Tenda 2012	Randomised clinical trial evaluating oral L-ornithine L-aspartate 3.7 g + branched-chain amino acids administered as a supplement either in daytime or in late evening. 32 participants with minimal hepatic encephalopathy. No differences between groups in clinical outcomes after 1 month. No serious adverse events occurred. No control group included.
Tiller 2016	Open, single-centre, observational study including 25 participants with overt hepatic encephalopathy. Evaluated motor function and found that administration of intravenous L-ornithine L-aspartate 20 g/day for 6 days improved dysdiadochocinesia and grasping movements.

n: number of participants.

DATA AND ANALYSES

Comparison 1. L-ornithine L-aspartate versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	19	1489	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.24, 0.72]
1.1 Low risk of bias	4	244	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.06, 3.58]
1.2 High risk of bias	15	1245	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.23, 0.72]
2 Mortality, by type of hepatic encephalopathy	19	1489	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.88]
2.1 Acute	6	597	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.40, 1.01]
2.2 Chronic	2	116	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

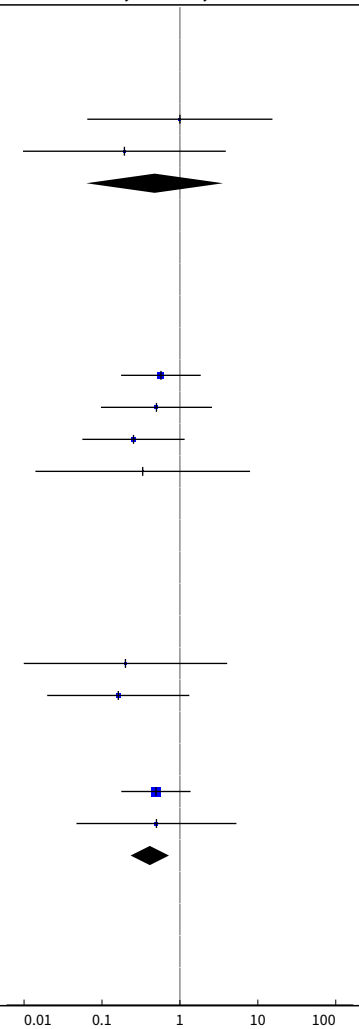
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Minimal	9	438	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.07, 1.94]
2.4 Prevention	5	338	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.18, 1.26]
3 Mortality, by administration method	19	1489	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.88]
3.1 Intravenous infusion	8	808	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 0.99]
3.2 Oral	11	681	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.19, 1.09]
4 Mortality, by publication status	19	1489	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.24, 0.72]
4.1 Full paper	14	1151	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.78]
4.2 Abstract	5	338	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.17, 1.18]
5 Hepatic encephalopathy	22	1375	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.59, 0.83]
5.1 Low risk of bias	1	63	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.07]
5.2 High risk of bias	21	1312	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.63, 0.79]
6 Hepatic encephalopathy, by type of hepatic encephalopathy	15	1255	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.50, 0.81]
6.1 Acute	5	550	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.91]
6.2 Chronic	2	116	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.28, 0.71]
6.3 Minimal	7	299	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.02]
6.4 Prevention	5	290	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.25, 0.72]
7 Hepatic encephalopathy, by administration method	22	1375	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.59, 0.83]
7.1 Intravenous infusion	11	784	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
7.2 Oral	11	591	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.50, 0.91]
8 Hepatic encephalopathy, by publication status	22	1375	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.59, 0.83]
8.1 Full paper	12	1032	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.85]
8.2 Abstract	3	225	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.25, 0.75]
8.3 Unpublished	7	118	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.03]
9 Hepatic encephalopathy, completeness status	22	1375	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.59, 0.83]

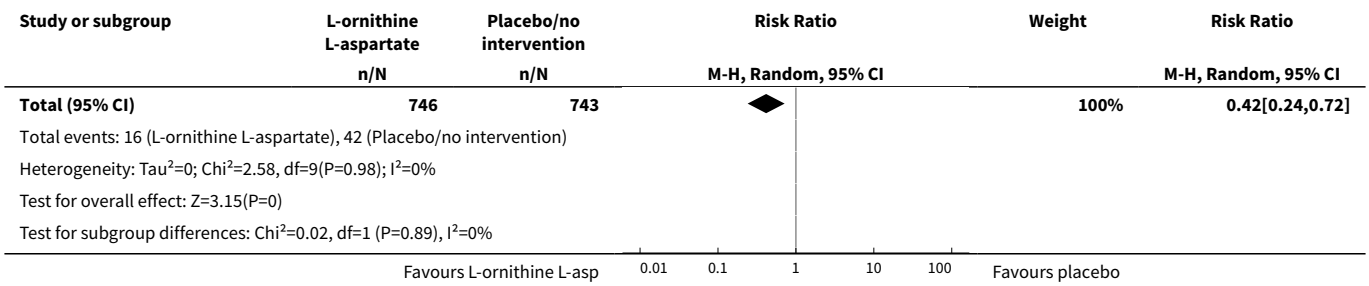
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Complete data	12	994	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.83]
9.2 Incomplete data	10	381	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.68, 0.97]
10 Serious adverse events	19	1489	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.90]
10.1 Low risk of bias	1	63	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.15, 4.65]
10.2 High risk of bias	18	1426	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.44, 0.89]
11 Serious adverse events, by type of hepatic encephalopathy	17	1283	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.97]
11.1 Acute overt	6	597	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.43, 1.00]
11.2 Chronic	2	192	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.19, 21.50]
11.3 Minimal	5	296	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.24, 1.38]
11.4 Prevention	4	198	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.17, 5.47]
12 Serious adverse events, by administration method	17	1283	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.97]
12.1 Intravenous infusion	8	808	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.46, 1.05]
12.2 Oral	9	475	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.23, 1.29]
13 Serious adverse events, by publication status	17	1283	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.97]
13.1 Full paper	13	1090	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.48, 1.02]
13.2 Abstract	4	193	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.34]
14 Non-serious adverse events	20	3158	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.91, 1.51]
14.1 Overall	14	1076	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.75, 1.77]
14.2 Diarrhoea	4	379	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.07, 24.18]
14.3 Flatulence	2	229	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.49, 5.18]
14.4 Nausea/vomiting	10	639	Risk Ratio (M-H, Random, 95% CI)	2.26 [1.25, 4.10]
14.5 Headaches	1	36	Risk Ratio (M-H, Random, 95% CI)	7.67 [0.39, 148.82]
14.6 Abdominal pain	3	318	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.23, 1.69]
14.7 Fever	2	233	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.12, 23.62]
14.8 Gastrointestinal	1	80	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.55, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.9 Pruritus	1	80	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.30, 1.21]
14.10 Fatigue	2	88	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.58, 1.18]
15 Blood ammonia concentrations	21		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 End of treatment	13	868	Mean Difference (IV, Random, 95% CI)	-18.52 [-33.63, -3.41]
15.2 Change from baseline	13	738	Mean Difference (IV, Random, 95% CI)	-12.94 [-20.04, -5.83]

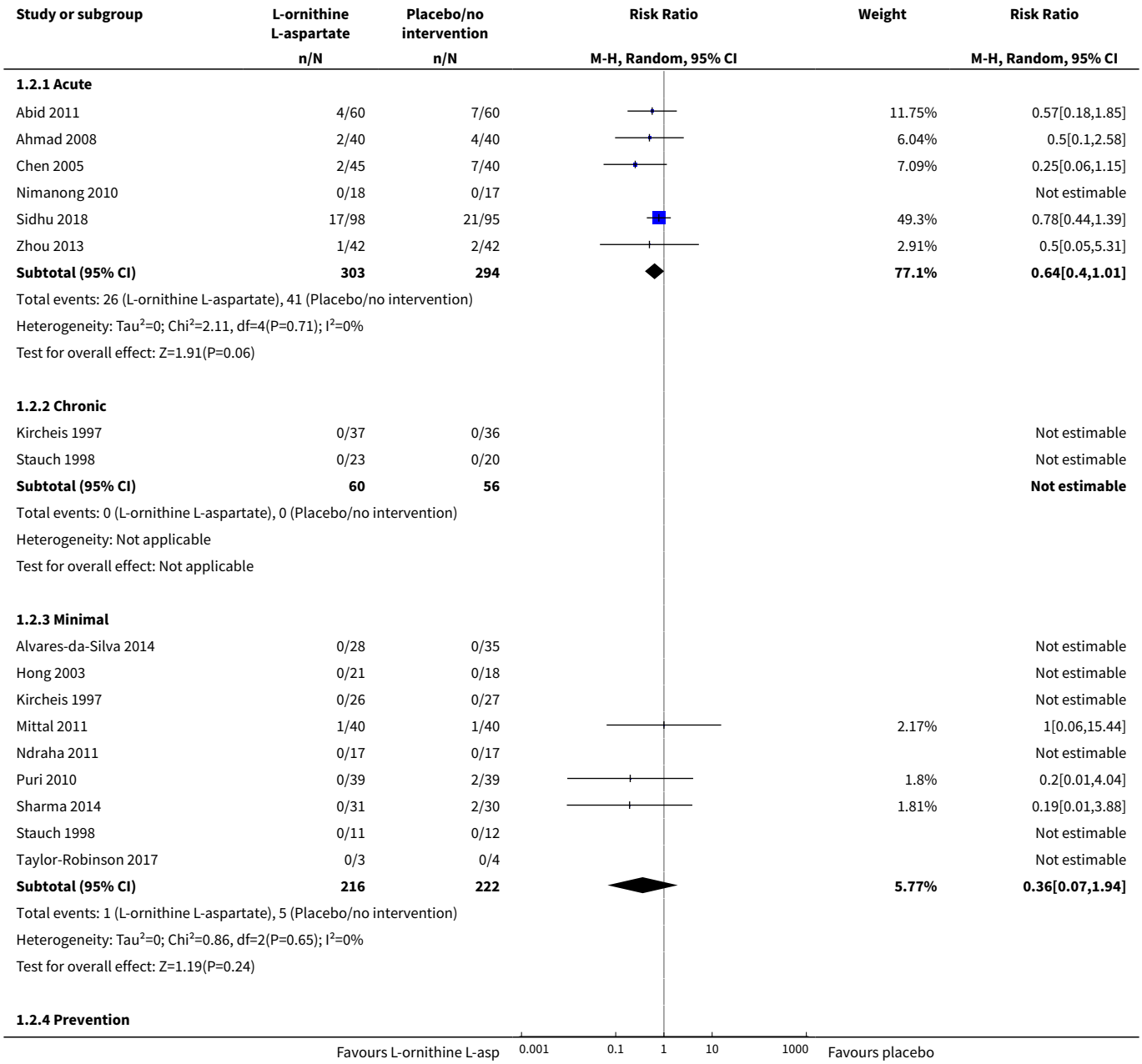
Analysis 1.1. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 1 Mortality.

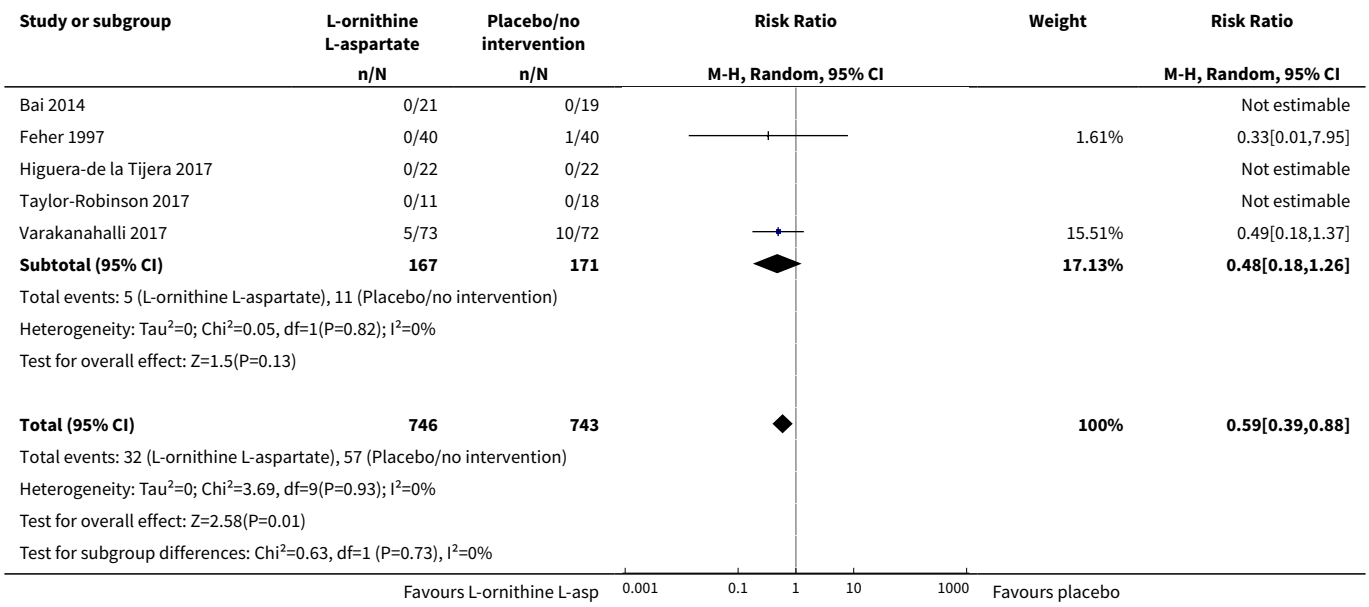
Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Low risk of bias					
Alvares-da-Silva 2014	0/28	0/35			Not estimable
Bai 2014	0/21	0/19			Not estimable
Mittal 2011	1/40	1/40		3.98%	1[0.06,15.44]
Sharma 2014	0/31	2/30		3.33%	0.19[0.01,3.88]
Subtotal (95% CI)	**120**	**124**		**7.31%**	**0.47[0.06,3.58]**
Total events: 1 (L-ornithine L-aspartate), 3 (Placebo/no intervention)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
1.1.2 High risk of bias					
Abid 2011	4/60	7/60		21.61%	0.57[0.18,1.85]
Ahmad 2008	2/40	4/40		11.1%	0.5[0.1,2.58]
Chen 2005	2/45	7/40		13.05%	0.25[0.06,1.15]
Feher 1997	0/40	1/40		2.97%	0.33[0.01,7.95]
Higuera-de la Tijera 2017	0/22	0/22			Not estimable
Hong 2003	0/21	0/18			Not estimable
Kircheis 1997	0/63	0/63			Not estimable
Ndraha 2011	0/17	0/17			Not estimable
Nimanong 2010	0/18	0/17			Not estimable
Puri 2010	0/39	2/39		3.31%	0.2[0.01,4.04]
Sidhu 2018	1/98	6/95		6.78%	0.16[0.02,1.32]
Stauch 1998	0/34	0/32			Not estimable
Taylor-Robinson 2017	0/14	0/22			Not estimable
Varakanahalli 2017	5/73	10/72		28.52%	0.49[0.18,1.37]
Zhou 2013	1/42	2/42		5.35%	0.5[0.05,5.31]
Subtotal (95% CI)	**626**	**619**		**92.69%**	**0.41[0.23,0.72]**
Total events: 15 (L-ornithine L-aspartate), 39 (Placebo/no intervention)					
Heterogeneity: Tau^2=0; Chi^2=1.92, df=7(P=0.96); I^2=0%					
Test for overall effect: Z=3.07(P=0)					



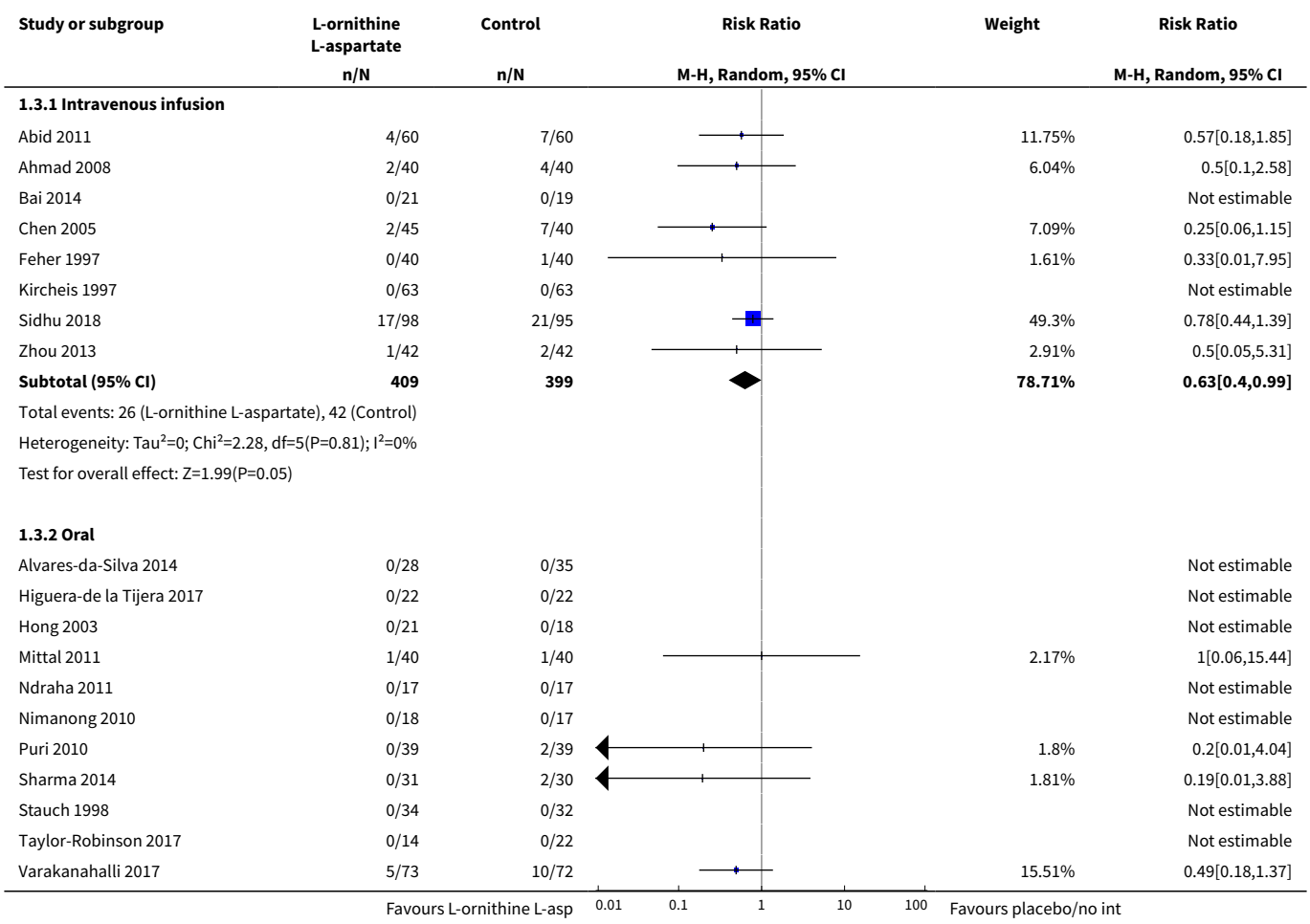


Analysis 1.2. Comparison 1 L-ornithine L-aspartate versus placebo/ no intervention, Outcome 2 Mortality, by type of hepatic encephalopathy.





Analysis 1.3. Comparison 1 L-ornithine L-aspartate versus placebo/ no intervention, Outcome 3 Mortality, by administration method.



Study or subgroup	L-ornithine L-aspartate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**337**	**344**		**21.29%**	**0.45[0.19,1.09]**
Total events: 6 (L-ornithine L-aspartate), 15 (Control)					
Heterogeneity: Tau²=0; Chi²=0.95, df=3(P=0.81); I²=0%					
Test for overall effect: Z=1.77(P=0.08)					
Total (95% CI)	**746**	**743**		**100%**	**0.59[0.39,0.88]**
Total events: 32 (L-ornithine L-aspartate), 57 (Control)					
Heterogeneity: Tau²=0; Chi²=3.69, df=9(P=0.93); I²=0%					
Test for overall effect: Z=2.58(P=0.01)					
Test for subgroup differences: Chi²=0.43, df=1 (P=0.51), I²=0%					

Favours L-ornithine L-asp 0.01 0.1 1 10 100 Favours placebo/no int

Analysis 1.4. Comparison 1 L-ornithine L-aspartate versus placebo/ no intervention, Outcome 4 Mortality, by publication status.

Study or subgroup	LOLA n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Full paper					
Abid 2011	4/60	7/60		21.61%	0.57[0.18,1.85]
Ahmad 2008	2/40	4/40		11.1%	0.5[0.1,2.58]
Alvares-da-Silva 2014	0/28	0/35			Not estimable
Bai 2014	0/21	0/19			Not estimable
Chen 2005	2/45	7/40		13.05%	0.25[0.06,1.15]
Feher 1997	0/40	1/40		2.97%	0.33[0.01,7.95]
Hong 2003	0/21	0/18			Not estimable
Kircheis 1997	0/63	0/63			Not estimable
Mittal 2011	1/40	1/40		3.98%	1[0.06,15.44]
Ndraha 2011	0/17	0/17			Not estimable
Sharma 2014	0/31	2/30		3.33%	0.19[0.01,3.88]
Sidhu 2018	1/98	6/95		6.78%	0.16[0.02,1.32]
Stauch 1998	0/34	0/32			Not estimable
Zhou 2013	1/42	2/42		5.35%	0.5[0.05,5.31]
Subtotal (95% CI)	**580**	**571**		**68.17%**	**0.4[0.21,0.78]**
Total events: 11 (LOLA), 30 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=2.22, df=7(P=0.95); I²=0%					
Test for overall effect: Z=2.71(P=0.01)					
1.4.2 Abstract					
Higuera-de la Tijera 2017	0/22	0/22			Not estimable
Nimanong 2010	0/18	0/17			Not estimable
Puri 2010	0/39	2/39		3.31%	0.2[0.01,4.04]
Taylor-Robinson 2017	0/14	0/22			Not estimable
Varakanahalli 2017	5/73	10/72		28.52%	0.49[0.18,1.37]
Subtotal (95% CI)	**166**	**172**		**31.83%**	**0.45[0.17,1.18]**
Total events: 5 (LOLA), 12 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.57); I²=0%					
Test for overall effect: Z=1.62(P=0.11)					

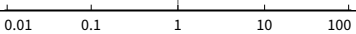
Favours L-ornithine L-asp 0.01 0.1 1 10 100 Favours placebo/no int

Study or subgroup	LOLA	Placebo/no intervention	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Total (95% CI)	**746**	**743**		**100%**	**0.42[0.24,0.72]**
Total events: 16 (LOLA), 42 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=2.58, df=9(P=0.98); I²=0%					
Test for overall effect: Z=3.15(P=0)					
Test for subgroup differences: Chi²=0.04, df=1 (P=0.85), I²=0%					

Favours L-ornithine L-asp | Favours placebo/no int

Analysis 1.5. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 5 Hepatic encephalopathy.

Study or subgroup	L-ornithine L-aspartate	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.5.1 Low risk of bias					
Alvares-da-Silva 2014	26/28	34/35		10.14%	0.96[0.85,1.07]
Subtotal (95% CI)	**28**	**35**		**10.14%**	**0.96[0.85,1.07]**
Total events: 26 (L-ornithine L-aspartate), 34 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
1.5.2 High risk of bias					
Higuera-de la Tijera 2017	5/22	12/22		2.95%	0.42[0.18,0.98]
Mittal 2011	26/40	36/40		8.72%	0.72[0.56,0.93]
Merz 1989a	9/11	9/10		7.46%	0.91[0.64,1.29]
Merz 1988a	10/21	13/21		5.05%	0.77[0.44,1.35]
Stauch 1998	17/34	24/32		6.91%	0.67[0.45,0.99]
Bai 2014	1/21	3/19		0.6%	0.3[0.03,2.66]
Merz 1987	3/4	5/6		4.12%	0.9[0.46,1.76]
Chen 2005	17/45	24/40		6.17%	0.63[0.4,0.99]
Varakanahalli 2017	9/73	20/72		3.78%	0.44[0.22,0.91]
Zhou 2013	7/42	11/42		3.02%	0.64[0.27,1.48]
Merz 1992a	7/8	8/8		7.65%	0.88[0.63,1.23]
Kircheis 1997	26/63	43/63		7.56%	0.6[0.43,0.85]
Sharma 2014	10/31	21/30		5.03%	0.46[0.26,0.81]
Merz 1988c	4/5	6/6		5.59%	0.81[0.49,1.34]
Taylor-Robinson 2017	0/14	1/22		0.3%	0.51[0.02,11.74]
Abid 2011	5/60	13/60		2.47%	0.38[0.15,1.01]
Ndraha 2011	0/17	0/17			Not estimable
Merz 1989b	3/5	4/5		3.05%	0.75[0.32,1.74]
Ahmad 2008	3/40	9/40		1.68%	0.33[0.1,1.14]
Sidhu 2018	24/98	25/95		5.82%	0.93[0.57,1.51]
Merz 1988b	2/4	3/4		1.93%	0.67[0.22,2.07]
Subtotal (95% CI)	**658**	**654**		**89.86%**	**0.71[0.63,0.79]**
Total events: 188 (L-ornithine L-aspartate), 290 (Control)					
Heterogeneity: Tau²=0; Chi²=19.05, df=19(P=0.45); I²=0.27%					
Test for overall effect: Z=6(P<0.0001)					
Total (95% CI)	**686**	**689**		**100%**	**0.7[0.59,0.83]**
Total events: 214 (L-ornithine L-aspartate), 324 (Control)					



Favours L-ornithine L-asp | Favours placebo/no int

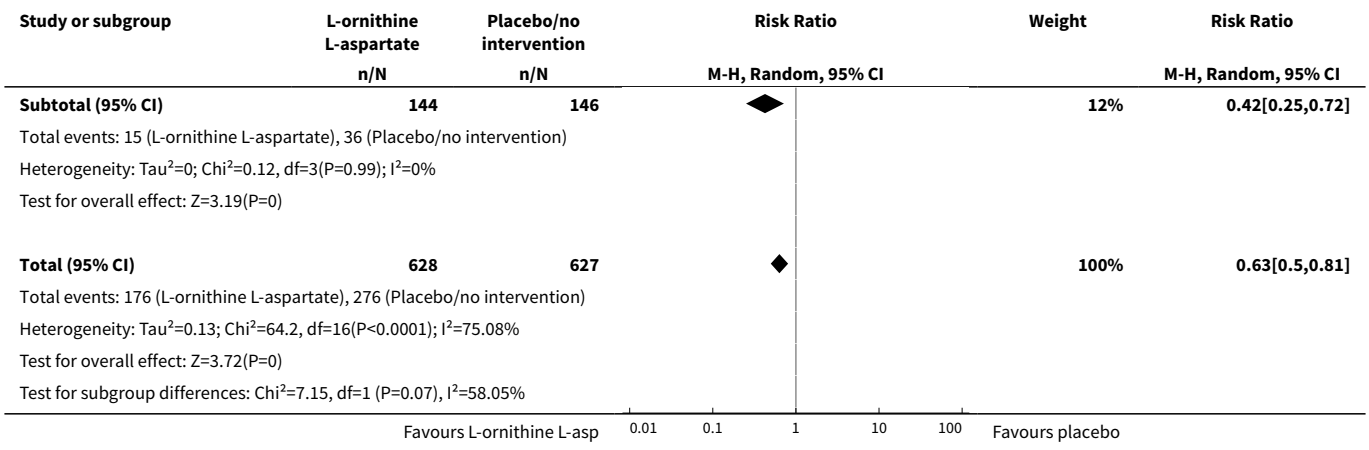
Study or subgroup	L-ornithine L-aspartate n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.07; Chi²=52.02, df=20(P=0); I²=61.56%					
Test for overall effect: Z=4.01(P<0.0001)					
Test for subgroup differences: Chi²=13.02, df=1 (P=0), I²=92.32%					

Favours L-ornithine L-asp 0.01 0.1 1 10 100 Favours placebo/no int

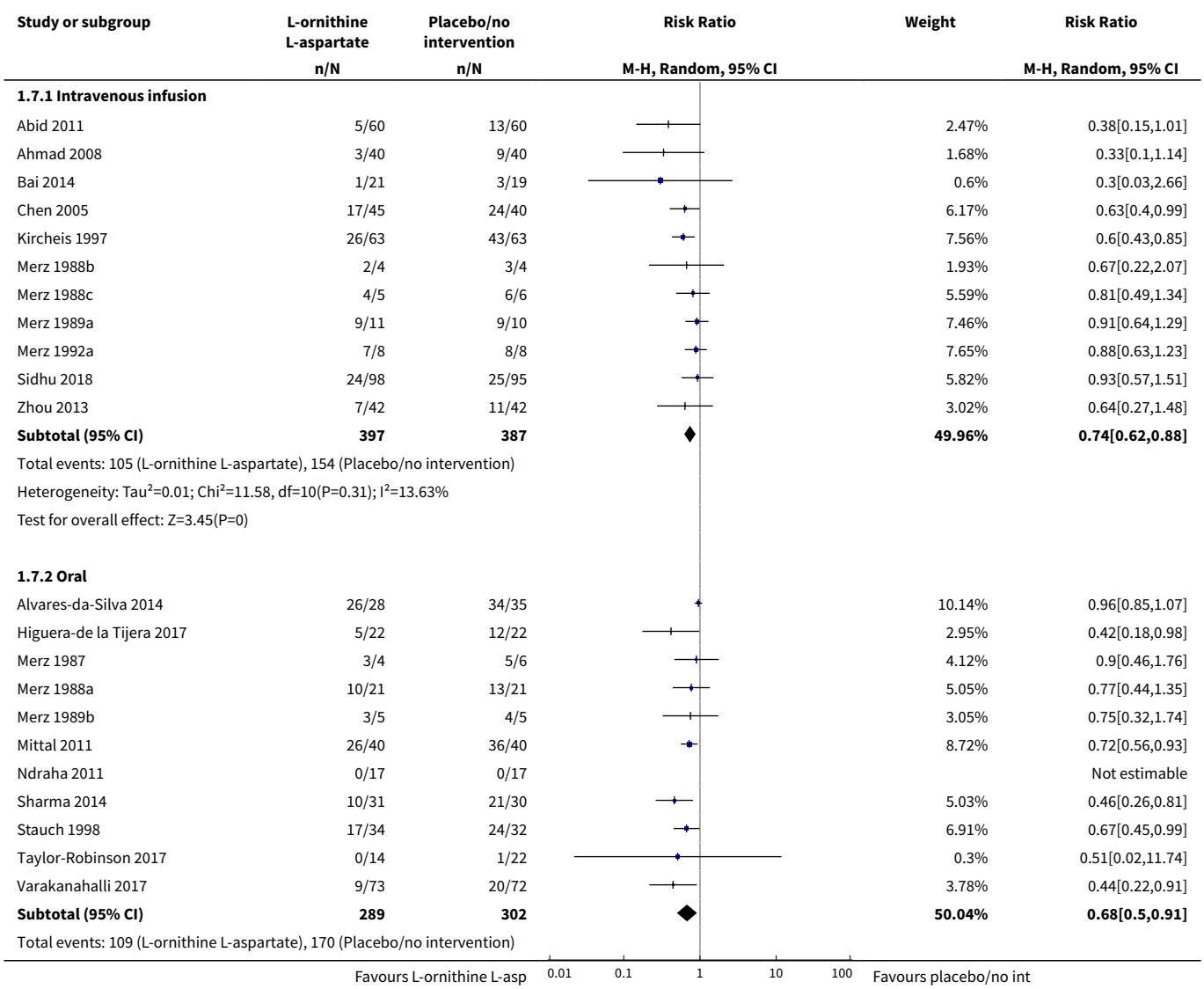
Analysis 1.6. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 6 Hepatic encephalopathy, by type of hepatic encephalopathy.

Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Acute					
Abid 2011	5/54	10/54		3.82%	0.5[0.18,1.37]
Ahmad 2008	3/40	9/40		2.87%	0.33[0.1,1.14]
Chen 2005	17/45	24/40		8.13%	0.63[0.4,0.99]
Sidhu 2018	24/98	25/95		7.81%	0.93[0.57,1.51]
Zhou 2013	7/42	11/42		4.74%	0.64[0.27,1.48]
Subtotal (95% CI)	**279**	**271**		**27.36%**	**0.69[0.51,0.91]**
Total events: 56 (L-ornithine L-aspartate), 79 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=3.4, df=4(P=0.49); I²=0%					
Test for overall effect: Z=2.59(P=0.01)					
1.6.2 Chronic					
Kircheis 1997	9/37	22/36		6.45%	0.4[0.21,0.74]
Stauch 1998	7/23	12/20		5.69%	0.51[0.25,1.04]
Subtotal (95% CI)	**60**	**56**		**12.14%**	**0.44[0.28,0.71]**
Total events: 16 (L-ornithine L-aspartate), 34 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=0.25, df=1(P=0.62); I²=0%					
Test for overall effect: Z=3.4(P=0)					
1.6.3 Minimal					
Abid 2011	0/6	3/6		0.71%	0.14[0.01,2.28]
Alvares-da-Silva 2014	26/28	34/35		11.1%	0.96[0.85,1.07]
Kircheis 1997	17/26	21/27		9.24%	0.84[0.6,1.19]
Mittal 2011	26/40	36/40		10.16%	0.72[0.56,0.93]
Sharma 2014	10/31	21/30		7.04%	0.46[0.26,0.81]
Stauch 1998	10/11	12/12		10.24%	0.91[0.72,1.16]
Taylor-Robinson 2017	0/3	0/4			Not estimable
Subtotal (95% CI)	**145**	**154**		**48.5%**	**0.78[0.6,1.02]**
Total events: 89 (L-ornithine L-aspartate), 127 (Placebo/no intervention)					
Heterogeneity: Tau²=0.07; Chi²=22.55, df=5(P=0); I²=77.82%					
Test for overall effect: Z=1.82(P=0.07)					
1.6.4 Prevention					
Bai 2014	1/21	3/19		1.11%	0.3[0.03,2.66]
Higuera-de la Tijera 2017	5/22	12/22		4.65%	0.42[0.18,0.98]
Ndraha 2011	0/17	0/17			Not estimable
Taylor-Robinson 2017	0/11	1/16		0.57%	0.47[0.02,10.63]
Varakanahalli 2017	9/73	20/72		5.68%	0.44[0.22,0.91]

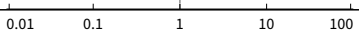
Favours L-ornithine L-asp 0.01 0.1 1 10 100 Favours placebo



Analysis 1.7. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 7 Hepatic encephalopathy, by administration method.



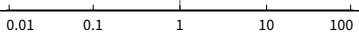
Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.14; Chi²=39.53, df=9(P<0.0001); I²=77.23%					
Test for overall effect: Z=2.55(P=0.01)					
Total (95% CI)	**686**	**689**		**100%**	**0.7[0.59,0.83]**
Total events: 214 (L-ornithine L-aspartate), 324 (Placebo/no intervention)					
Heterogeneity: Tau²=0.07; Chi²=52.02, df=20(P=0); I²=61.56%					
Test for overall effect: Z=4.01(P<0.0001)					
Test for subgroup differences: Chi²=0.26, df=1 (P=0.61), I²=0%					



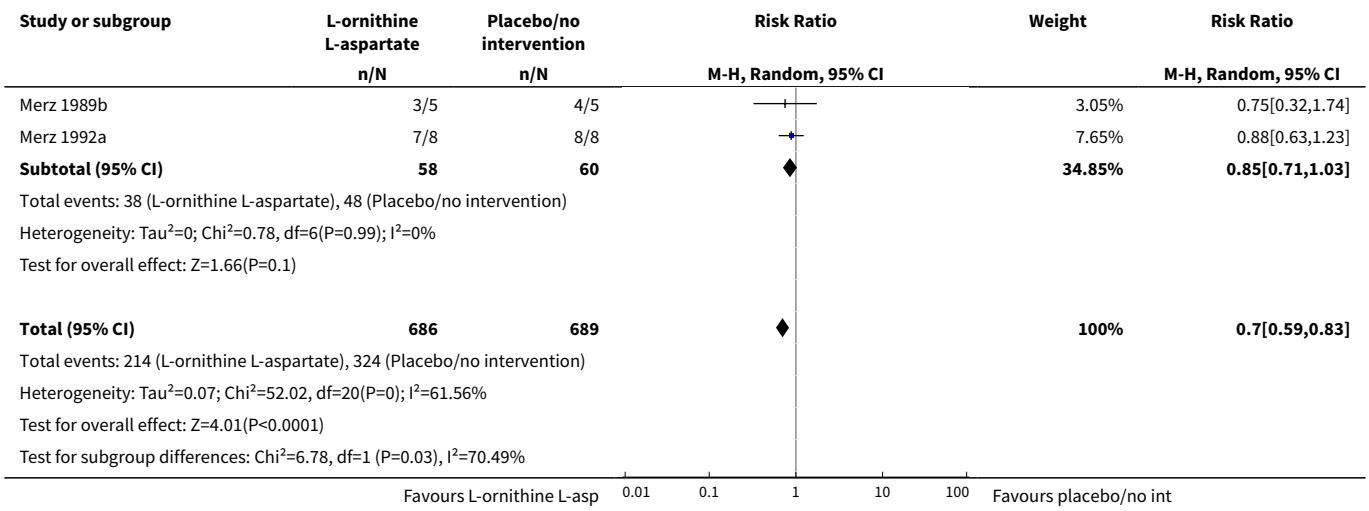
Favours L-ornithine L-asp — Favours placebo/no int

Analysis 1.8. Comparison 1 L-ornithine L-aspartate versus placebo/ no intervention, Outcome 8 Hepatic encephalopathy, by publication status.

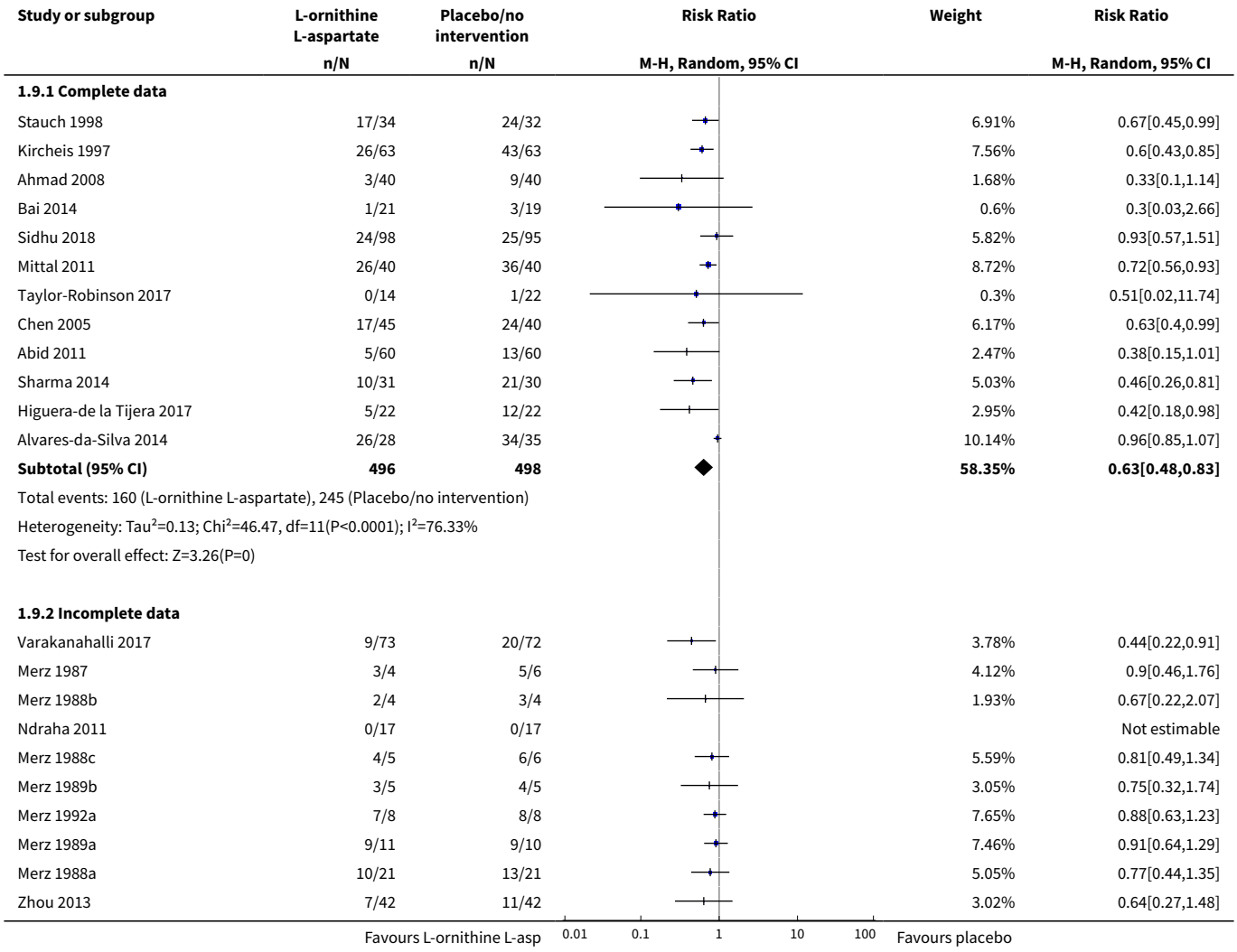
Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Full paper					
Abid 2011	5/60	13/60		2.47%	0.38[0.15,1.01]
Ahmad 2008	3/40	9/40		1.68%	0.33[0.1,1.14]
Alvares-da-Silva 2014	26/28	34/35		10.14%	0.96[0.85,1.07]
Bai 2014	1/21	3/19		0.6%	0.3[0.03,2.66]
Chen 2005	17/45	24/40		6.17%	0.63[0.4,0.99]
Kircheis 1997	26/63	43/63		7.56%	0.6[0.43,0.85]
Mittal 2011	26/40	36/40		8.72%	0.72[0.56,0.93]
Ndraha 2011	0/17	0/17			Not estimable
Sharma 2014	10/31	21/30		5.03%	0.46[0.26,0.81]
Sidhu 2018	24/98	25/95		5.82%	0.93[0.57,1.51]
Stauch 1998	17/34	24/32		6.91%	0.67[0.45,0.99]
Zhou 2013	7/42	11/42		3.02%	0.64[0.27,1.48]
Subtotal (95% CI)	**519**	**513**		**58.12%**	**0.65[0.5,0.85]**
Total events: 162 (L-ornithine L-aspartate), 243 (Placebo/no intervention)					
Heterogeneity: Tau²=0.12; Chi²=41.92, df=10(P<0.0001); I²=76.15%					
Test for overall effect: Z=3.13(P=0)					
1.8.2 Abstract					
Higuera-de la Tijera 2017	5/22	12/22		2.95%	0.42[0.18,0.98]
Taylor-Robinson 2017	0/14	1/22		0.3%	0.51[0.02,11.74]
Varakanahalli 2017	9/73	20/72		3.78%	0.44[0.22,0.91]
Subtotal (95% CI)	**109**	**116**		**7.03%**	**0.43[0.25,0.75]**
Total events: 14 (L-ornithine L-aspartate), 33 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=0.02, df=2(P=0.99); I²=0%					
Test for overall effect: Z=3.01(P=0)					
1.8.3 Unpublished					
Merz 1987	3/4	5/6		4.12%	0.9[0.46,1.76]
Merz 1988a	10/21	13/21		5.05%	0.77[0.44,1.35]
Merz 1988b	2/4	3/4		1.93%	0.67[0.22,2.07]
Merz 1988c	4/5	6/6		5.59%	0.81[0.49,1.34]
Merz 1989a	9/11	9/10		7.46%	0.91[0.64,1.29]

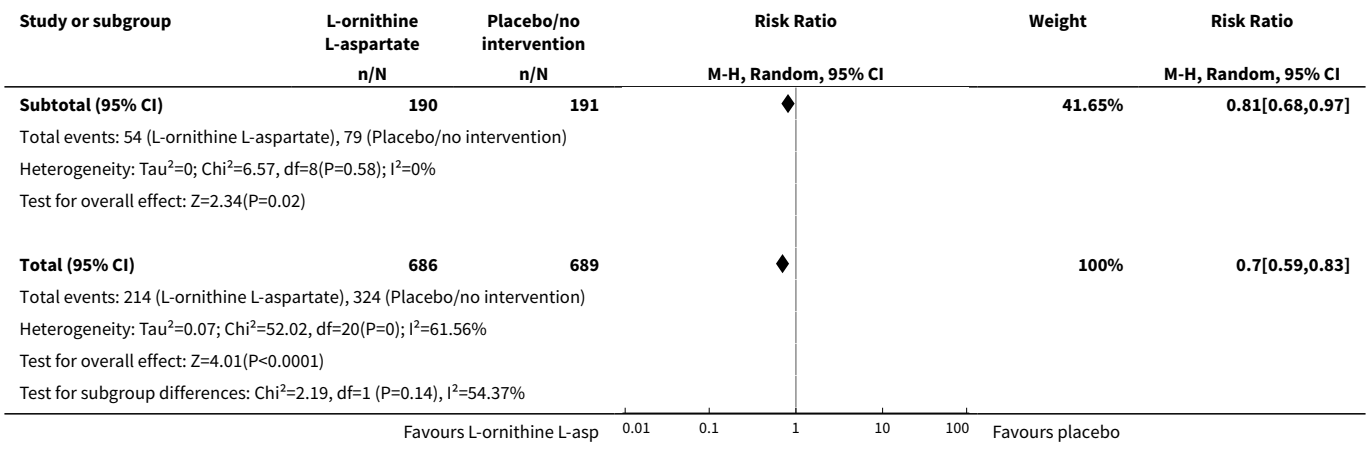


Favours L-ornithine L-asp — Favours placebo/no int

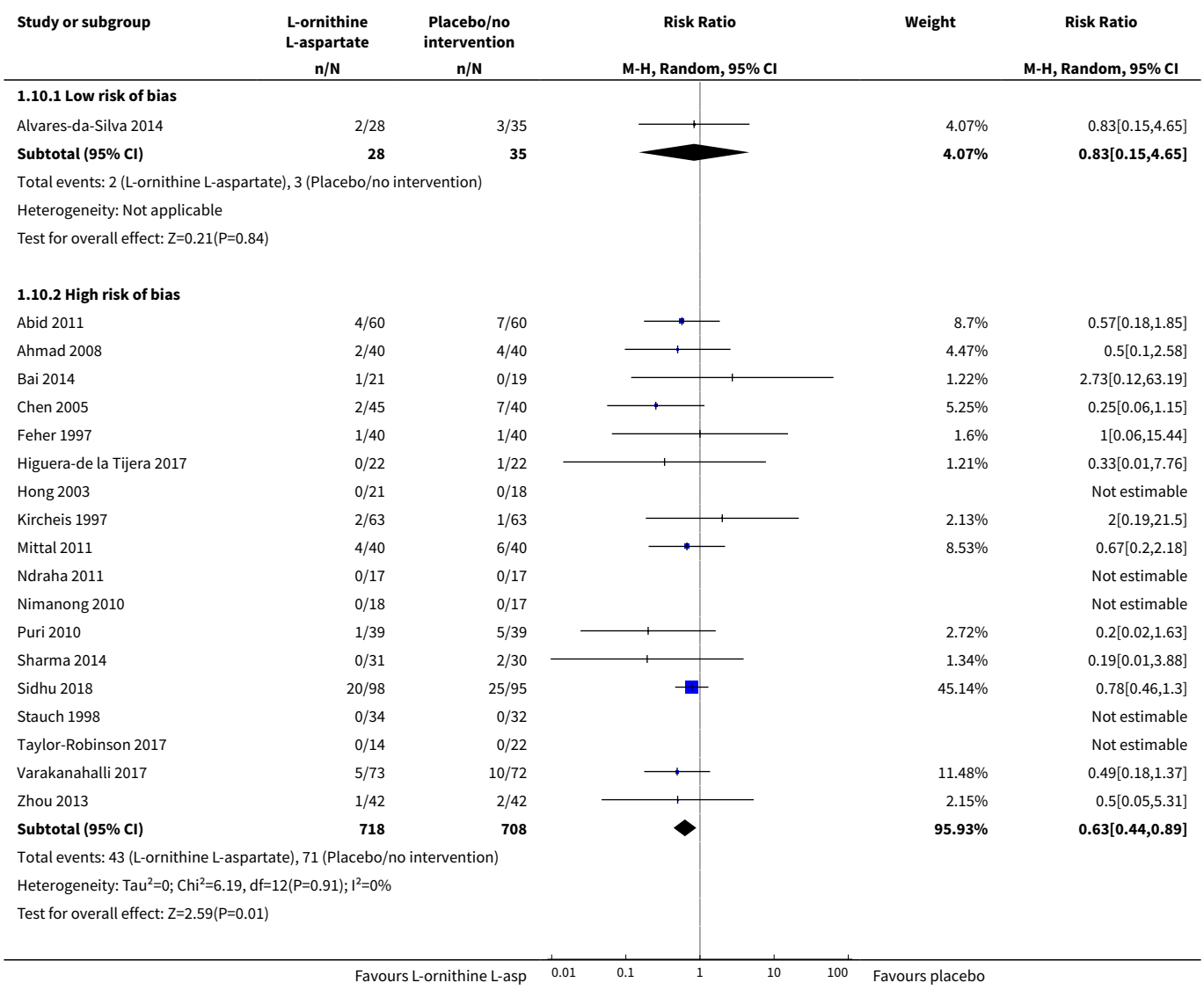


Analysis 1.9. Comparison 1 L-ornithine L-aspartate versus placebo/ no intervention, Outcome 9 Hepatic encephalopathy, completeness status.





Analysis 1.10. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 10 Serious adverse events.

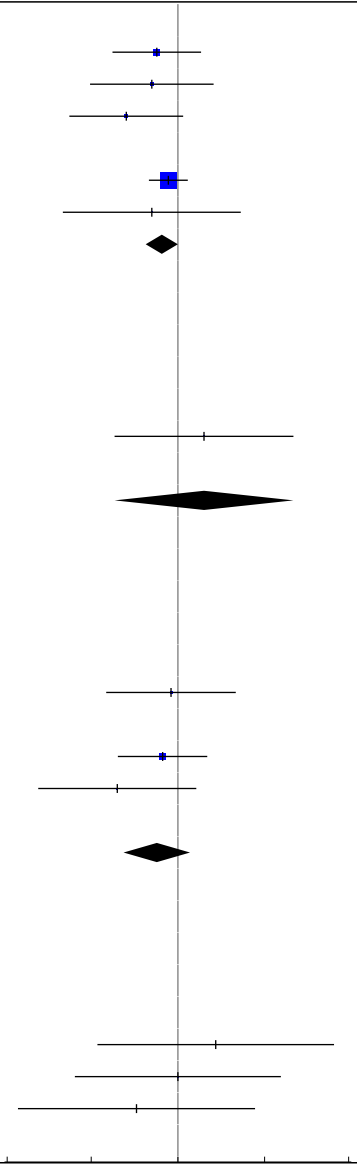


Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**746**	**743**		**100%**	**0.63[0.45,0.9]**
Total events: 45 (L-ornithine L-aspartate), 74 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=6.29, df=13(P=0.93); I²=0%					
Test for overall effect: Z=2.58(P=0.01)					
Test for subgroup differences: Chi²=0.1, df=1 (P=0.75), I²=0%					

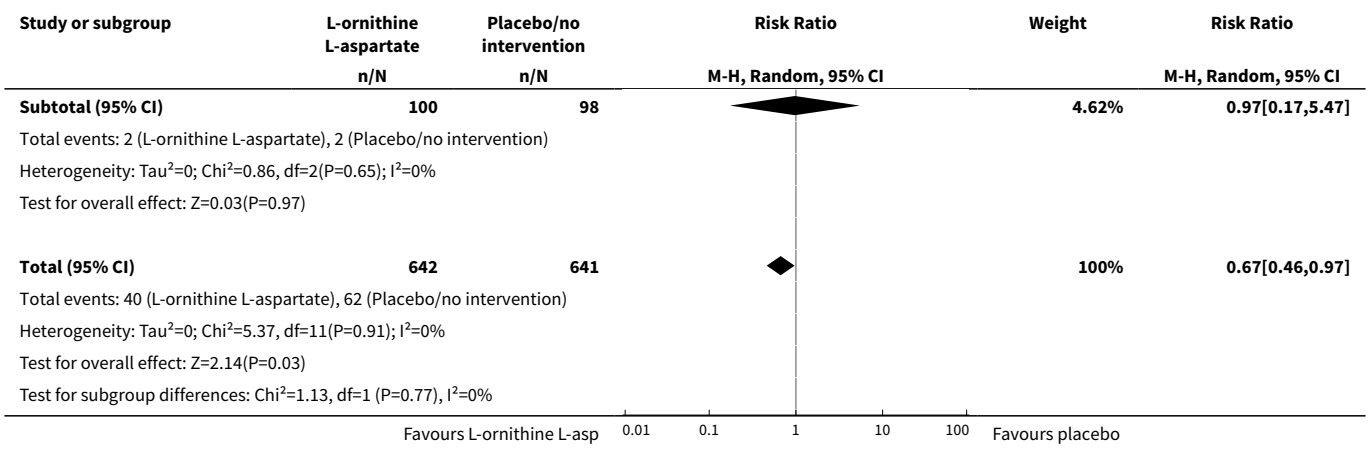
Favours L-ornithine L-asp | Favours placebo

Analysis 1.11. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 11 Serious adverse events, by type of hepatic encephalopathy.

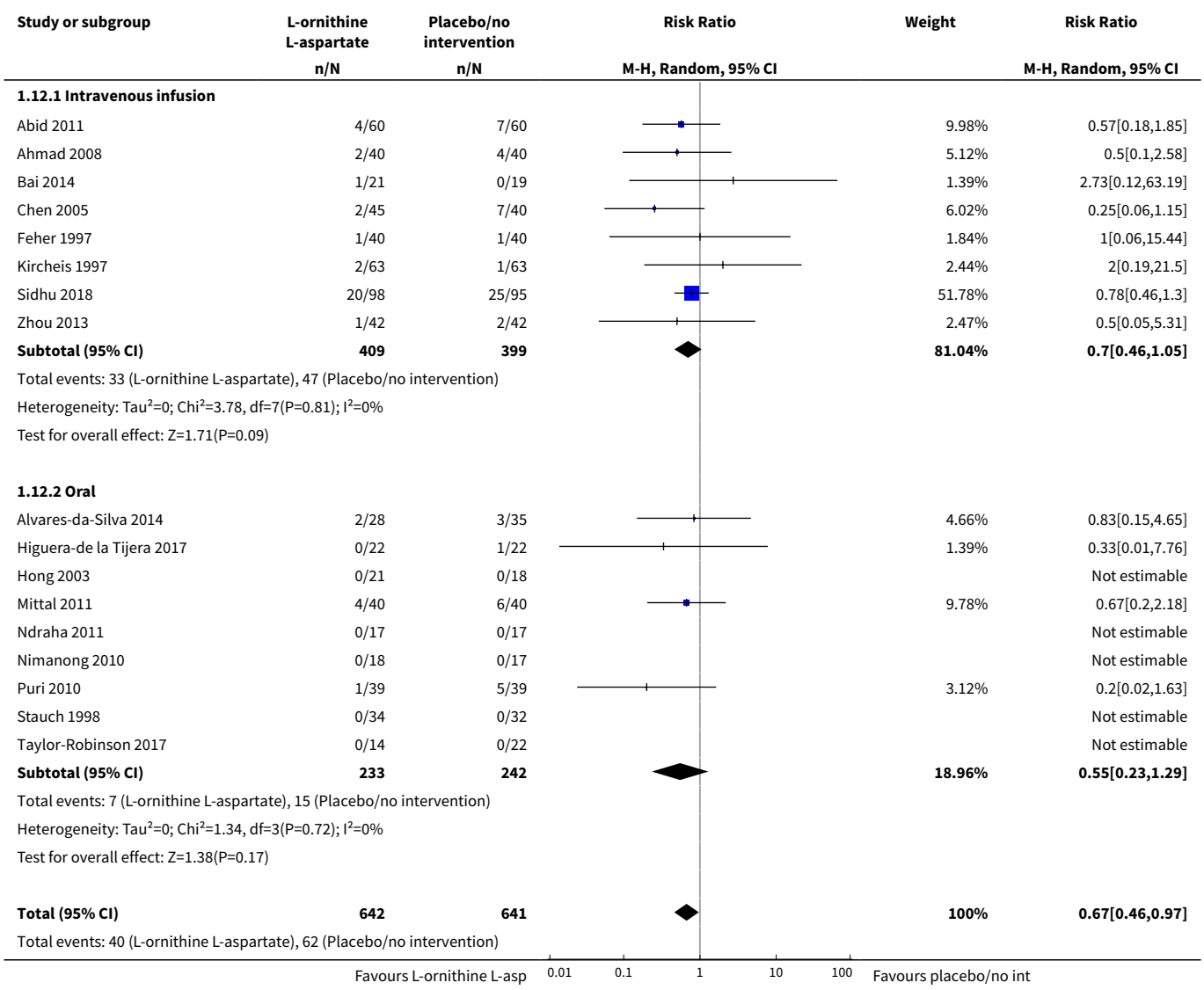
Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Acute overt					
Abid 2011	4/60	7/60		9.98%	0.57[0.18,1.85]
Ahmad 2008	2/40	4/40		5.12%	0.5[0.1,2.58]
Chen 2005	2/45	7/40		6.02%	0.25[0.06,1.15]
Nimanong 2010	0/18	0/17			Not estimable
Sidhu 2018	20/98	25/95		51.78%	0.78[0.46,1.3]
Zhou 2013	1/42	2/42		2.47%	0.5[0.05,5.31]
Subtotal (95% CI)	**303**	**294**		**75.37%**	**0.65[0.43,1]**
Total events: 29 (L-ornithine L-aspartate), 45 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=2.16, df=4(P=0.71); I²=0%					
Test for overall effect: Z=1.96(P=0.05)					
1.11.2 Chronic					
Kircheis 1997	2/63	1/63		2.44%	2[0.19,21.5]
Stauch 1998	0/34	0/32			Not estimable
Subtotal (95% CI)	**97**	**95**		**2.44%**	**2[0.19,21.5]**
Total events: 2 (L-ornithine L-aspartate), 1 (Placebo/no intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
1.11.3 Minimal					
Alvares-da-Silva 2014	2/28	3/35		4.66%	0.83[0.15,4.65]
Hong 2003	0/21	0/18			Not estimable
Mittal 2011	4/40	6/40		9.78%	0.67[0.2,2.18]
Puri 2010	1/39	5/39		3.12%	0.2[0.02,1.63]
Taylor-Robinson 2017	0/14	0/22			Not estimable
Subtotal (95% CI)	**142**	**154**		**17.57%**	**0.57[0.24,1.38]**
Total events: 7 (L-ornithine L-aspartate), 14 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=1.24, df=2(P=0.54); I²=0%					
Test for overall effect: Z=1.24(P=0.22)					
1.11.4 Prevention					
Bai 2014	1/21	0/19		1.39%	2.73[0.12,63.19]
Feher 1997	1/40	1/40		1.84%	1[0.06,15.44]
Higuera-de la Tijera 2017	0/22	1/22		1.39%	0.33[0.01,7.76]
Ndraha 2011	0/17	0/17			Not estimable



Favours L-ornithine L-asp | Favours placebo



Analysis 1.12. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 12 Serious adverse events, by administration method.

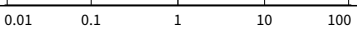


Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=5.37, df=11(P=0.91); I²=0%					
Test for overall effect: Z=2.14(P=0.03)					
Test for subgroup differences: Chi²=0.25, df=1 (P=0.62), I²=0%					

Favours L-ornithine L-asp | Favours placebo/no int

Analysis 1.13. Comparison 1 L-ornithine L-aspartate versus placebo/ no intervention, Outcome 13 Serious adverse events, by publication status.

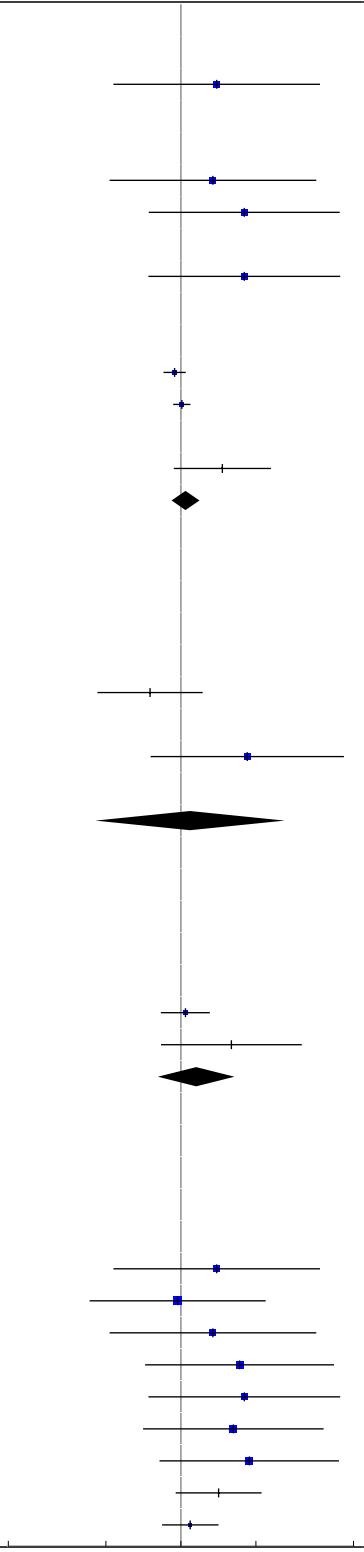
Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Full paper					
Abid 2011	4/60	7/60		9.98%	0.57[0.18,1.85]
Ahmad 2008	2/40	4/40		5.12%	0.5[0.1,2.58]
Alvares-da-Silva 2014	2/28	3/35		4.66%	0.83[0.15,4.65]
Bai 2014	1/21	0/19		1.39%	2.73[0.12,63.19]
Chen 2005	2/45	7/40		6.02%	0.25[0.06,1.15]
Feher 1997	1/40	1/40		1.84%	1[0.06,15.44]
Hong 2003	0/21	0/18			Not estimable
Kircheis 1997	2/63	1/63		2.44%	2[0.19,21.5]
Mittal 2011	4/40	6/40		9.78%	0.67[0.2,2.18]
Ndraha 2011	0/17	0/17			Not estimable
Sidhu 2018	20/98	25/95		51.78%	0.78[0.46,1.3]
Stauch 1998	0/34	0/32			Not estimable
Zhou 2013	1/42	2/42		2.47%	0.5[0.05,5.31]
Subtotal (95% CI)	**549**	**541**		**95.49%**	**0.7[0.48,1.02]**
Total events: 39 (L-ornithine L-aspartate), 56 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=3.82, df=9(P=0.92); I²=0%					
Test for overall effect: Z=1.84(P=0.07)					
1.13.2 Abstract					
Higuera-de la Tijera 2017	0/22	1/22		1.39%	0.33[0.01,7.76]
Nimanong 2010	0/18	0/17			Not estimable
Puri 2010	1/39	5/39		3.12%	0.2[0.02,1.63]
Taylor-Robinson 2017	0/14	0/22			Not estimable
Subtotal (95% CI)	**93**	**100**		**4.51%**	**0.23[0.04,1.34]**
Total events: 1 (L-ornithine L-aspartate), 6 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.79); I²=0%					
Test for overall effect: Z=1.63(P=0.1)					
Total (95% CI)	**642**	**641**		**100%**	**0.67[0.46,0.97]**
Total events: 40 (L-ornithine L-aspartate), 62 (Placebo/no intervention)					
Heterogeneity: Tau²=0; Chi²=5.37, df=11(P=0.91); I²=0%					
Test for overall effect: Z=2.14(P=0.03)					
Test for subgroup differences: Chi²=1.44, df=1 (P=0.23), I²=30.73%					

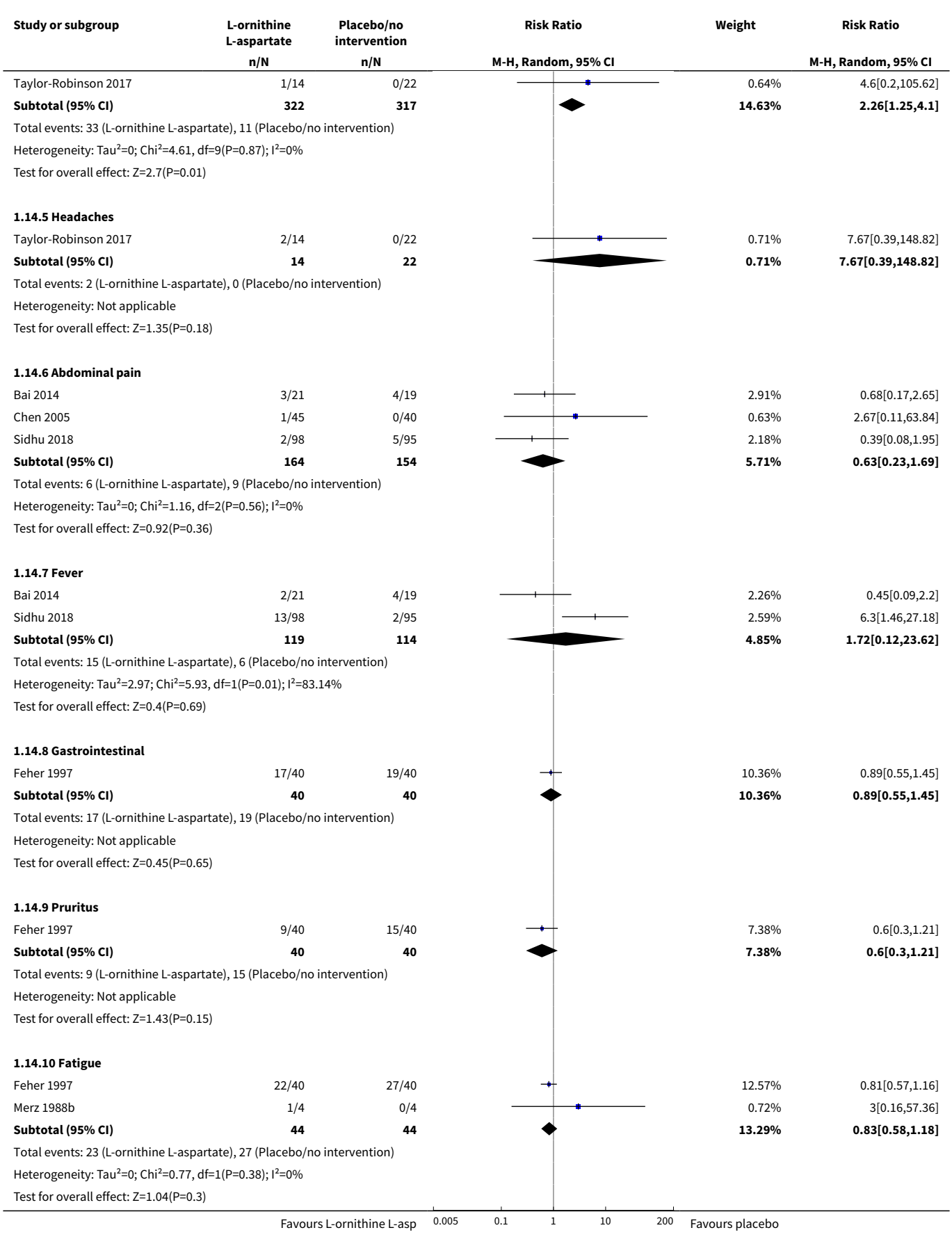


Favours L-ornithine L-asp | Favours placebo/no int

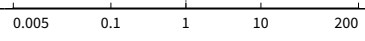
Analysis 1.14. Comparison 1 L-ornithine L-aspartate versus placebo/no intervention, Outcome 14 Non-serious adverse events.

Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Overall					
Abid 2011	0/60	0/60			Not estimable
Ahmad 2008	1/40	0/40		0.63%	3[0.13,71.51]
Alvares-da-Silva 2014	0/28	0/35			Not estimable
Blanco Vela 2011c	0/15	0/16			Not estimable
Chen 2005	1/45	0/40		0.63%	2.67[0.11,63.84]
Feher 1997	3/40	0/40		0.73%	7[0.37,131.28]
Higuera-de la Tijera 2017	0/22	0/22			Not estimable
Kircheis 1997	3/63	0/63		0.72%	7[0.37,132.79]
Mittal 2011	0/40	0/40			Not estimable
Ndraha 2011	0/17	0/17			Not estimable
Schmid 2010	14/20	17/20		12.79%	0.82[0.59,1.16]
Sidhu 2018	53/98	50/95		14.06%	1.03[0.79,1.34]
Stauch 1998	0/34	0/32			Not estimable
Taylor-Robinson 2017	5/14	2/20		2.5%	3.57[0.8,15.86]
Subtotal (95% CI)	**536**	**540**		**32.05%**	**1.15[0.75,1.77]**
Total events: 80 (L-ornithine L-aspartate), 69 (Placebo/no intervention)					
Heterogeneity: Tau^2=0.09; Chi^2=10.07, df=6(P=0.12); I^2=40.42%					
Test for overall effect: Z=0.65(P=0.52)					
1.14.2 Diarrhoea					
Sidhu 2018	2/98	5/95		2.18%	0.39[0.08,1.95]
Stauch 1998	0/34	0/32			Not estimable
Taylor-Robinson 2017	2/14	0/22		0.71%	7.67[0.39,148.82]
Zhou 2013	0/42	0/42			Not estimable
Subtotal (95% CI)	**188**	**191**		**2.89%**	**1.32[0.07,24.18]**
Total events: 4 (L-ornithine L-aspartate), 5 (Placebo/no intervention)					
Heterogeneity: Tau^2=3.05; Chi^2=3.06, df=1(P=0.08); I^2=67.29%					
Test for overall effect: Z=0.19(P=0.85)					
1.14.3 Flatulence					
Sidhu 2018	13/98	11/95		6.81%	1.15[0.54,2.43]
Taylor-Robinson 2017	3/14	1/22		1.29%	4.71[0.54,40.95]
Subtotal (95% CI)	**112**	**117**		**8.11%**	**1.6[0.49,5.18]**
Total events: 16 (L-ornithine L-aspartate), 12 (Placebo/no intervention)					
Heterogeneity: Tau^2=0.32; Chi^2=1.48, df=1(P=0.22); I^2=32.22%					
Test for overall effect: Z=0.78(P=0.44)					
1.14.4 Nausea/vomiting					
Ahmad 2008	1/40	0/40		0.63%	3[0.13,71.51]
Bai 2014	1/21	1/19		0.85%	0.9[0.06,13.48]
Chen 2005	1/45	0/40		0.63%	2.67[0.11,63.84]
Hong 2003	3/21	0/18		0.74%	6.05[0.33,109.75]
Kircheis 1997	3/63	0/63		0.72%	7[0.37,132.79]
Merz 1988b	2/4	0/4		0.81%	5[0.31,79.94]
Merz 1988c	3/5	0/6		0.82%	8.17[0.52,128.42]
Merz 1989a	7/11	2/10		3.07%	3.18[0.85,11.88]
Sidhu 2018	11/98	8/95		5.72%	1.33[0.56,3.17]





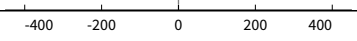
Study or subgroup	L-ornithine L-aspartate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**1579**	**1579**		**100%**	**1.17[0.91,1.51]**
Total events: 205 (L-ornithine L-aspartate), 173 (Placebo/no intervention)					
Heterogeneity: Tau^2=0.1; Chi^2=44.8, df=30(P=0.04); I^2=33.04%					
Test for overall effect: Z=1.21(P=0.23)					
Test for subgroup differences: Chi^2=14.49, df=1 (P=0.11), I^2=37.88%					



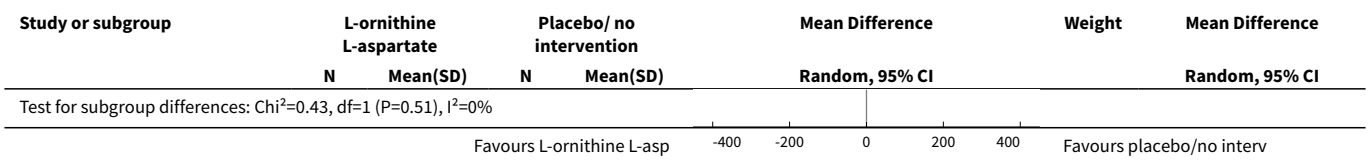
Favours L-ornithine L-asp — Favours placebo

Analysis 1.15. Comparison 1 L-ornithine L-aspartate versus placebo/ no intervention, Outcome 15 Blood ammonia concentrations.

Study or subgroup	L-ornithine L-aspartate N	Mean(SD)	Placebo/ no intervention N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.15.1 End of treatment							
Ahmad 2008	40	44.4 (14.8)	40	65.6 (27.2)		8.6%	-21.13[-30.73,-11.53]
Chen 2005	45	50.9 (6.7)	40	112.6 (7.2)		8.88%	-61.7[-64.67,-58.73]
Feher 1997	40	52.5 (30.6)	40	63.5 (28.9)		8.35%	-11[-24.04,2.04]
Hong 2003	21	34.6 (7.3)	18	38.7 (9.7)		8.81%	-4.1[-9.56,1.36]
Kircheis 1997	63	64 (76)	63	78 (83)		6.85%	-14[-41.79,13.79]
Merz 1988b	4	73 (24)	4	88 (10.8)		7.07%	-15[-40.79,10.79]
Merz 1988c	5	47 (14.3)	6	65.6 (34.8)		6.53%	-18.6[-49.14,11.94]
Merz 1989a	11	75.5 (60.6)	10	80.1 (47.4)		4.85%	-4.6[-50.92,41.72]
Puri 2010	39	85.2 (18.2)	39	83.8 (17)		8.7%	1.35[-6.46,9.16]
Schmid 2010	20	50.4 (27.6)	20	69.1 (29.4)		7.94%	-18.7[-36.37,-1.03]
Sidhu 2018	98	40.3 (33.8)	95	60.7 (35.1)		8.59%	-20.44[-30.17,-10.71]
Stauch 1998	11	52.2 (27.8)	12	71.2 (55.9)		5.96%	-19[-54.64,16.64]
Zhou 2013	42	51.3 (7.7)	42	76.5 (5.4)		8.88%	-25.17[-28.02,-22.32]
Subtotal ***	**439**		**429**			**100%**	**-18.52[-33.63,-3.41]**
Heterogeneity: Tau^2=667.22; Chi^2=601.72, df=12(P<0.0001); I^2=98.01%							
Test for overall effect: Z=2.4(P=0.02)							
1.15.2 Change from baseline							
Abid 2011	60	-18.8 (52.1)	60	-8.7 (85)		5.27%	-10.1[-35.33,15.13]
Alvares-da-Silva 2014	28	5 (24.1)	35	8.5 (26.7)		10.55%	-3.5[-16.07,9.07]
Bai 2014	21	2.6 (19.9)	19	23.8 (22.2)		10.25%	-21.2[-34.32,-8.08]
Kircheis 1997	63	-17.3 (37)	63	-6 (32)		10.83%	-11.3[-23.38,0.78]
Merz 1987	4	-5.5 (31.6)	5	-11.4 (29.6)		2.58%	5.9[-34.5,46.3]
Merz 1988b	4	0 (24.5)	4	15.3 (14.4)		4.6%	-15.3[-43.15,12.55]
Merz 1989a	10	-28 (59)	9	3.2 (24.7)		2.63%	-31.2[-71.17,8.77]
Merz 1989b	5	-8.6 (8.6)	5	-7.6 (9.4)		11.34%	-1[-12.17,10.17]
Merz 1992a	7	-157 (185)	8	-2.9 (23.1)		0.26%	-154.1[-292.08,-16.12]
Mittal 2011	40	-9.6 (9.3)	40	-0.5 (7.8)		15.1%	-9.09[-12.85,-5.33]
Schmid 2010	20	-15 (40.1)	20	11.1 (36.6)		5.69%	-26.1[-49.89,-2.31]
Stauch 1998	33	-27.5 (40.5)	30	-24.3 (49.8)		6.09%	-3.2[-25.75,19.35]
Varakanahalli 2017	73	-23.6 (14.8)	72	1.4 (13.3)		14.79%	-24.99[-29.57,-20.41]
Subtotal ***	**368**		**370**			**100%**	**-12.94[-20.04,-5.83]**
Heterogeneity: Tau^2=83.25; Chi^2=45.41, df=12(P<0.0001); I^2=73.57%							
Test for overall effect: Z=3.57(P=0)							



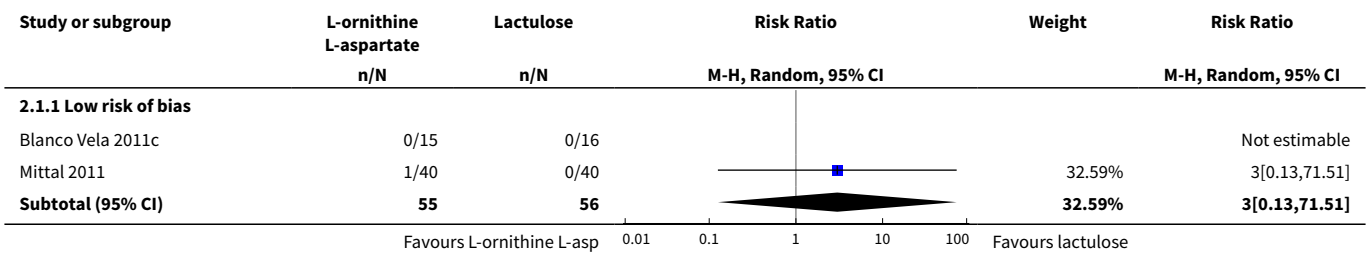
Favours L-ornithine L-asp — Favours placebo/no interv

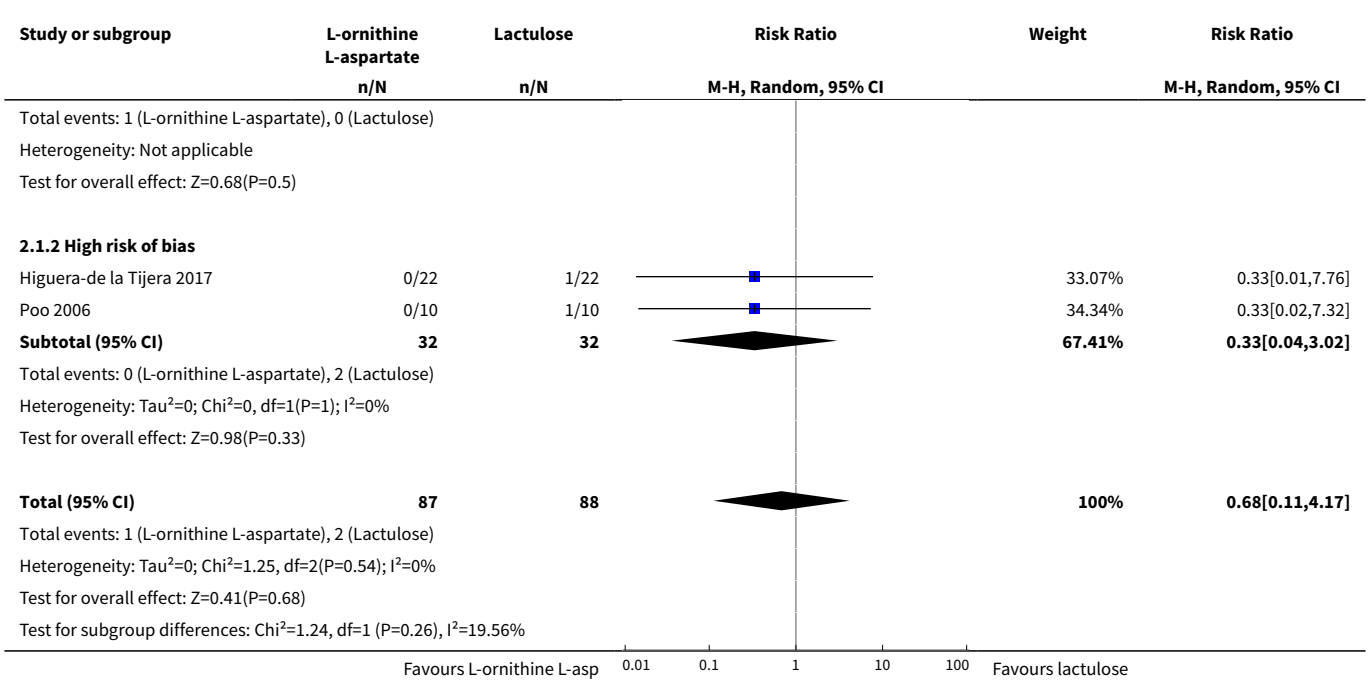


Comparison 2. L-ornithine L-aspartate versus lactulose

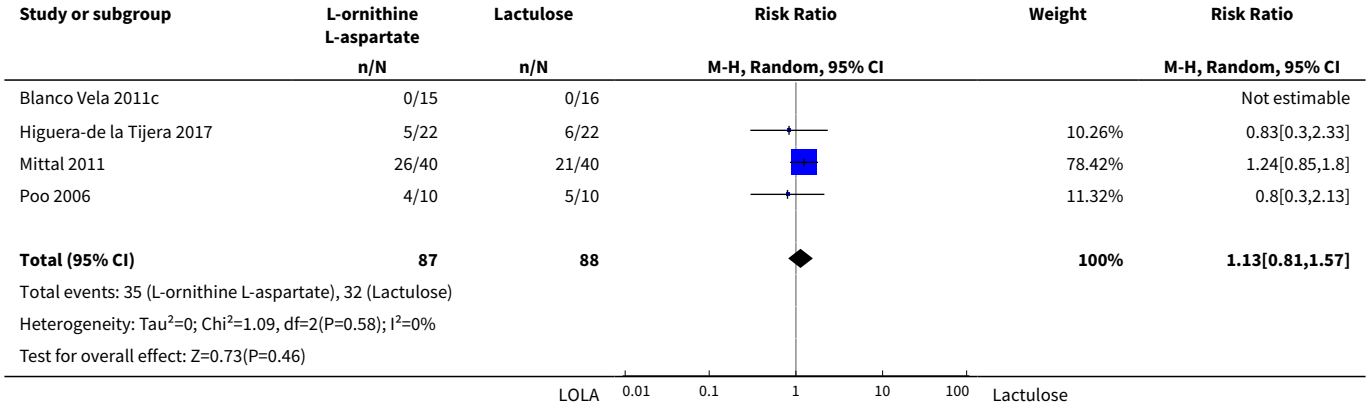
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	4	175	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.11, 4.17]
1.1 Low risk of bias	2	111	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 71.51]
1.2 High risk of bias	2	64	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.02]
2 Hepatic encephalopathy	4	175	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.81, 1.57]
3 Serious adverse events	3	144	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.22, 2.11]
4 Non-serious adverse events	2	292	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.18]
4.1 Overall	1	80	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.13]
4.2 Diarrhoea	1	44	Risk Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.54]
4.3 Bloating	1	44	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.77]
4.4 Flatulence	1	44	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.77]
4.5 Abdominal pain/discomfort	1	80	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.13]
5 Blood ammonia end of treatment	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 End of treatment	2	51	Mean Difference (IV, Fixed, 95% CI)	-3.26 [-10.60, 4.09]
5.2 Change from baseline	1	80	Mean Difference (IV, Fixed, 95% CI)	-1.14 [-4.54, 2.26]

Analysis 2.1. Comparison 2 L-ornithine L-aspartate versus lactulose, Outcome 1 Mortality.

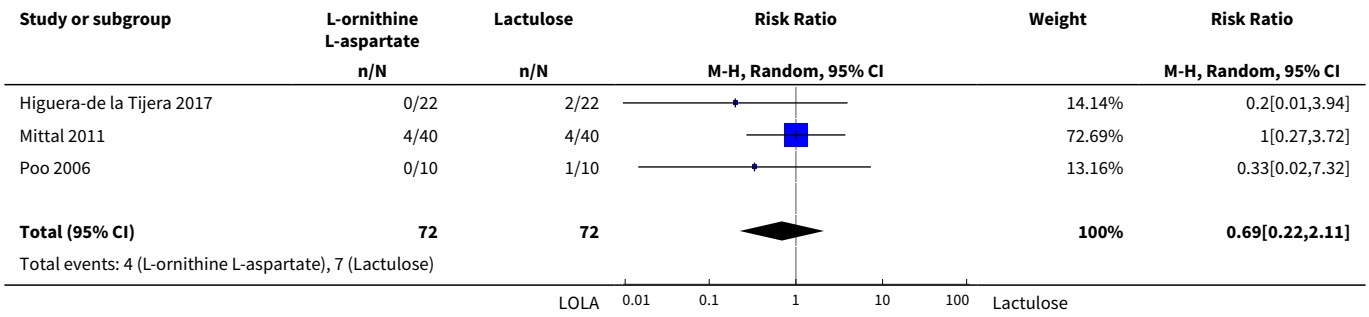




Analysis 2.2. Comparison 2 L-ornithine L-aspartate versus lactulose, Outcome 2 Hepatic encephalopathy.



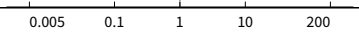
Analysis 2.3. Comparison 2 L-ornithine L-aspartate versus lactulose, Outcome 3 Serious adverse events.



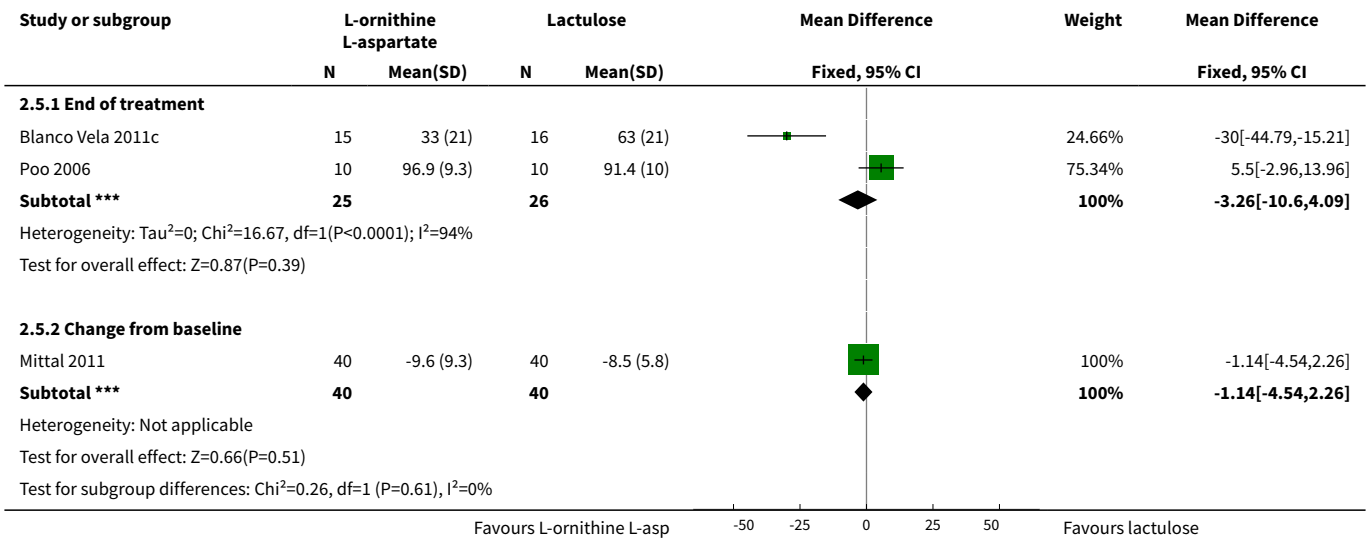
Study or subgroup	L-ornithine L-aspartate n/N	Lactulose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=1.21, df=2(P=0.55); I²=0%					
Test for overall effect: Z=0.65(P=0.52)					

Analysis 2.4. Comparison 2 L-ornithine L-aspartate versus lactulose, Outcome 4 Non-serious adverse events.

Study or subgroup	L-ornithine L-aspartate n/N	Lactulose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Overall					
Mittal 2011	0/40	7/40		19.5%	0.07[0,1.13]
Subtotal (95% CI)	**40**	**40**		**19.5%**	**0.07[0,1.13]**
Total events: 0 (L-ornithine L-aspartate), 7 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					
2.4.2 Diarrhoea					
Higuera-de la Tijera 2017	0/22	14/22		20.51%	0.03[0,0.54]
Subtotal (95% CI)	**22**	**22**		**20.51%**	**0.03[0,0.54]**
Total events: 0 (L-ornithine L-aspartate), 14 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.39(P=0.02)					
2.4.3 Bloating					
Higuera-de la Tijera 2017	0/22	10/22		20.24%	0.05[0,0.77]
Subtotal (95% CI)	**22**	**22**		**20.24%**	**0.05[0,0.77]**
Total events: 0 (L-ornithine L-aspartate), 10 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.15(P=0.03)					
2.4.4 Flatulence					
Higuera-de la Tijera 2017	0/22	10/22		20.24%	0.05[0,0.77]
Subtotal (95% CI)	**22**	**22**		**20.24%**	**0.05[0,0.77]**
Total events: 0 (L-ornithine L-aspartate), 10 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.15(P=0.03)					
2.4.5 Abdominal pain/discomfort					
Mittal 2011	0/40	7/40		19.5%	0.07[0,1.13]
Subtotal (95% CI)	**40**	**40**		**19.5%**	**0.07[0,1.13]**
Total events: 0 (L-ornithine L-aspartate), 7 (Lactulose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.88(P=0.06)					
Total (95% CI)	**146**	**146**		**100%**	**0.05[0.01,0.18]**
Total events: 0 (L-ornithine L-aspartate), 48 (Lactulose)					
Heterogeneity: Tau²=0; Chi²=0.15, df=4(P=1); I²=0%					
Test for overall effect: Z=4.67(P<0.0001)					
Test for subgroup differences: Chi²=0.15, df=1 (P=1), I²=0%					



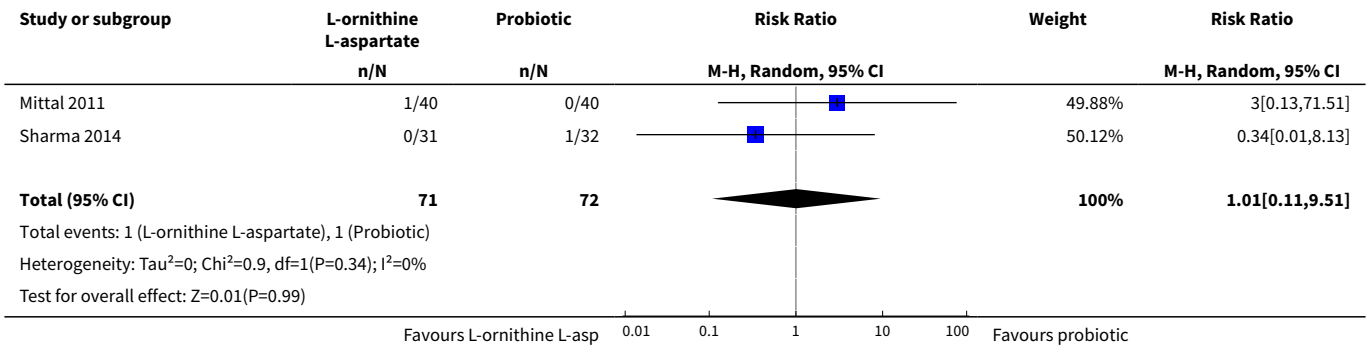
Analysis 2.5. Comparison 2 L-ornithine L-aspartate versus lactulose, Outcome 5 Blood ammonia end of treatment.



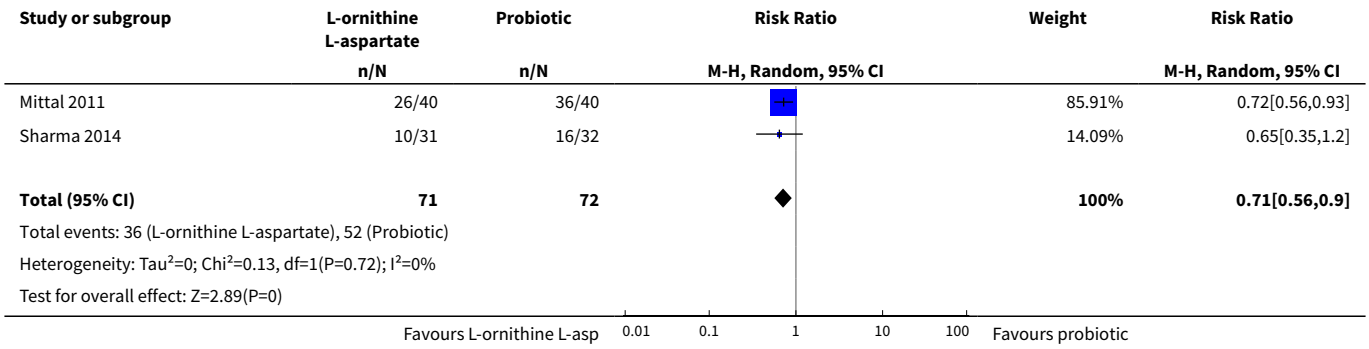
Comparison 3. L-ornithine L-aspartate versus probiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	143	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.11, 9.51]
2 Hepatic encephalopathy	2	143	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.56, 0.90]
3 Serious adverse events	2	143	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.23, 4.88]
4 Ammonia (change from baseline)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

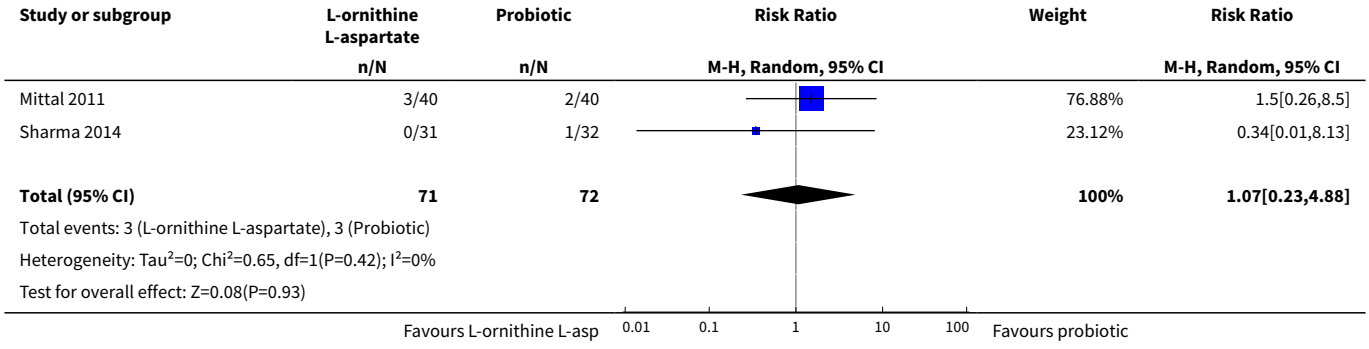
Analysis 3.1. Comparison 3 L-ornithine L-aspartate versus probiotic, Outcome 1 Mortality.



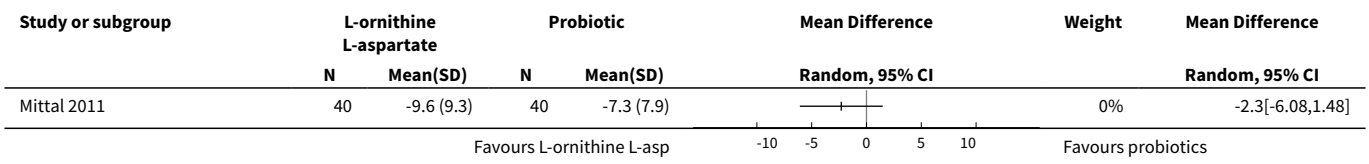
Analysis 3.2. Comparison 3 L-ornithine L-aspartate versus probiotic, Outcome 2 Hepatic encephalopathy.



Analysis 3.3. Comparison 3 L-ornithine L-aspartate versus probiotic, Outcome 3 Serious adverse events.



Analysis 3.4. Comparison 3 L-ornithine L-aspartate versus probiotic, Outcome 4 Ammonia (change from baseline).

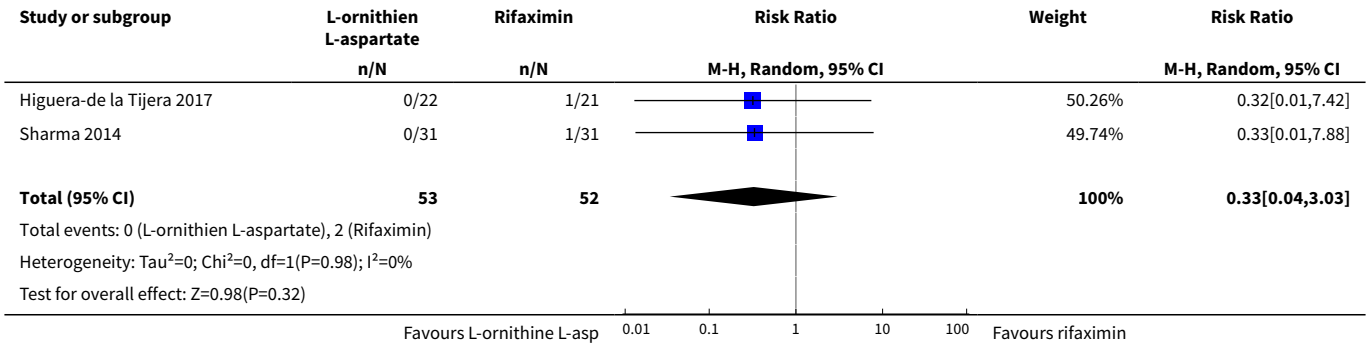


Comparison 4. L-ornithine L-aspartate versus rifaximin

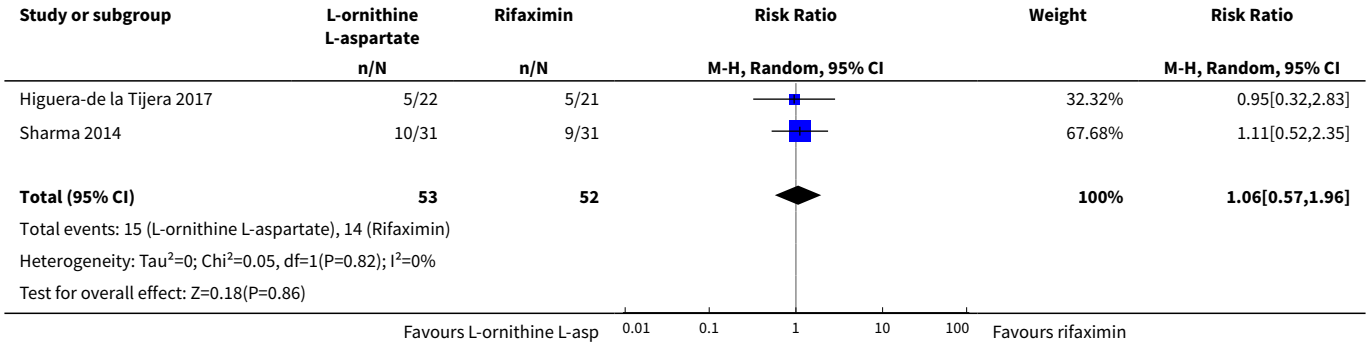
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	105	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.03]
2 Hepatic encephalopathy	2	105	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.57, 1.96]
3 Serious adverse events	1	43	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Non-serious adverse events	1	43	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.42]
4.1 Nausea/vomiting	1	43	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.42]

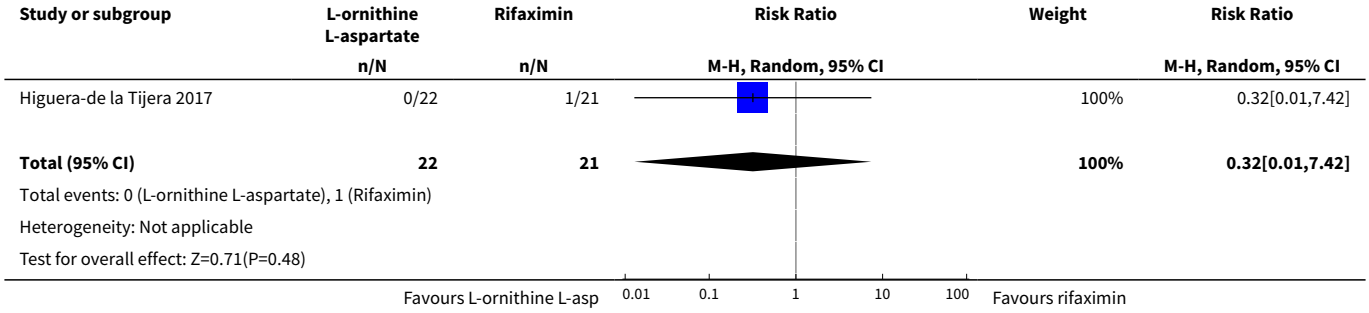
Analysis 4.1. Comparison 4 L-ornithine L-aspartate versus rifaximin, Outcome 1 Mortality.



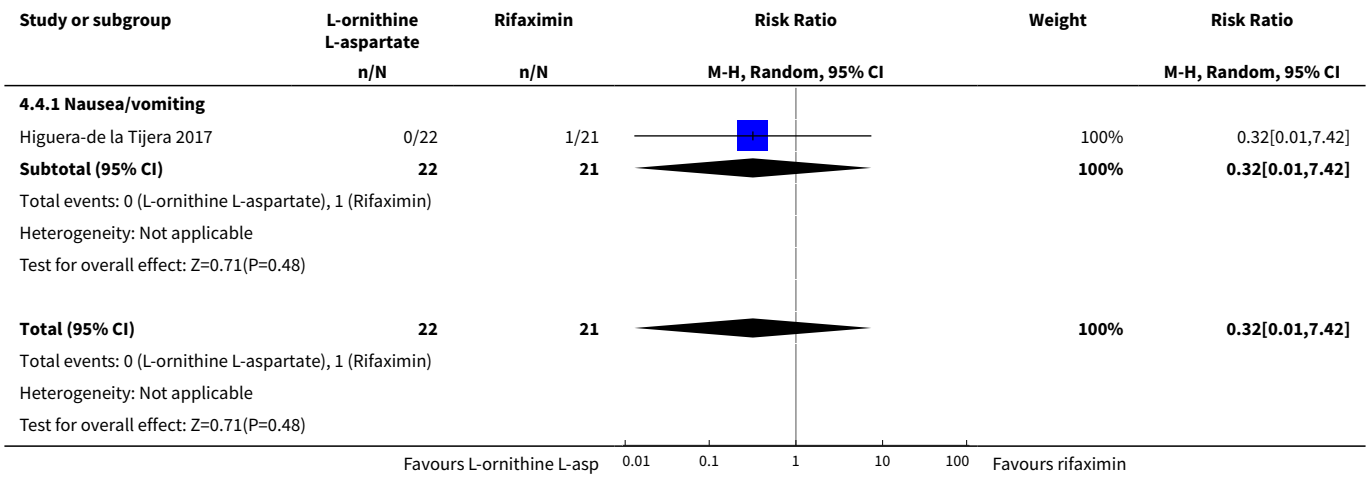
Analysis 4.2. Comparison 4 L-ornithine L-aspartate versus rifaximin, Outcome 2 Hepatic encephalopathy.



Analysis 4.3. Comparison 4 L-ornithine L-aspartate versus rifaximin, Outcome 3 Serious adverse events.



Analysis 4.4. Comparison 4 L-ornithine L-aspartate versus rifaximin, Outcome 4 Non-serious adverse events.



ADDITIONAL TABLES

Table 1. Definitions and assessment of neuropsychiatric status in the include studies with corresponding recommended definitions in the EASL/AASLD guidelines

Study and date	Definition of hepatic encephalopathy		Assessment of neuropsychiatric status
	Study material (publication)	EASL/AASLD guideline	
Abid 2011	Minimal	Minimal	• Mental status (West Haven Criteria) • Number Connection Test-A • Venous blood ammonia
	Acute: Grade I to IV	Episodic	
Ahmad 2008	Acute: Grade I to III	Episodic	• Mental status (West Haven Criteria) • Postprandial venous blood ammonia
Alvares-da-Silva 2014	Minimal	Minimal	• Number Connection Tests-A and -B • Digital Symbol Test • Mini Mental Score Examination • Critical Flicker Frequency • Electroencephalogram (every third participant only) • Arterial blood ammonia
Bai 2014[1]	Unimpaired	Unimpaired	• Mental status (West Haven Criteria) • Number Connection Test-A • Serial Dotting Test • Line Tracing Test • Fasting and postprandial venous blood ammonia
Blanco Vela 2011c[2]	Acute: Grade III or IV	Overt	• Mental status (West Haven Criteria) • Glasgow Coma Scale • Clinical hepatic encephalopathy staging scale (CHESS)

Table 1. Definitions and assessment of neuropsychiatric status in the include studies with corresponding recommended definitions in the EASL/AASLD guidelines *(Continued)*

			• Asterixis • Number Connection Test-A • Plasma ammonia • Portal systemic encephalopathy score and index[3]
Chen 2005	Acute: Grade I to IV	Episodic	• Mental status (West Haven Criteria) • Blood ammonia
Feher 1997[1,2]	Unimpaired	Unimpaired	• Mental status (clinical examination) • Number Connection Test-A • Fasting and postprandial venous blood ammonia
Fleig 1999[2]	Minimal	Minimal	• Mental status (West Haven Criteria) • Number Connection Tests -A and -B • Digit Symbol Test • Line Tracing Test • Serial Dotting Test • Psychometric hepatic encephalopathy score (PHES)
	Chronic Grade I or II	Persistent	
Hasan 2012[2]	Minimal	Minimal	• Mental status • Critical Flicker Frequency • Blood ammonia
	Chronic: Grade I or II	Persistent	
Higuera-de la Tijera 2017[1]	Unimpaired	Unimpaired	• Mental status (West Haven Criteria) • Psychometric hepatic encephalopathy score (PHES) • Critical Flicker Fusion Frequency
Hong 2003[2]	Minimal	Minimal	• Number Connection Test • Critical Flicker Frequency • Blood ammonia
Kircheis 1997	Minimal	Minimal	• Mental status (West Haven Criteria) • Asterixis • Number Connection Test-A • Fasting and postprandial venous blood ammonia • Portal Systemic Encephalopathy Sum & Index[3]
	Chronic: Grade I or II	Persistent	
Maldonado 2010[2]	Minimal	Minimal	• Blood ammonia at baseline and 60 minutes after a 10g post-glutamine load
Merz 1987	Minimal	Minimal	• Hepatic encephalopathy grade • Number Connection Test • Blood ammonia
	Overt	Unclear	
Merz 1988a	Minimal	Minimal	• Hepatic encephalopathy grade • Number Connection Test • Blood ammonia
	Overt	Unclear	
Merz 1988b	Minimal	Minimal	• Mental status (Holms grade) • Number Connection Test-A • Fasting and postprandial venous blood ammonia and post-prandial arterial blood ammonia
	Acute	Episodic	

Table 1. Definitions and assessment of neuropsychiatric status in the include studies with corresponding recommended definitions in the EASL/AASLD guidelines *(Continued)*

Merz 1988c	Minimal	Minimal	• Mental status (West Haven Criteria) • Number Connection Test-A • Postprandial venous blood ammonia
	Overt	Unclear	
Merz 1988d[2]	Unknown	Unknown	• Unknown
Merz 1989a	Minimal	Minimal	• Mental status (Holms grade) • Number Connection Test-A • Fasting and postprandial venous blood ammonia
	Overt	Unclear	
Merz 1989b	Minimal	Minimal	• Hepatic encephalopathy grade • Number Connection Test • Blood ammonia
	Overt	Unclear	
Merz 1992a	Minimal	Minimal	• Mental status • Fasting blood ammonia
	Overt	Unclear	
Merz 1994a[2]	Minimal	Minimal	• Mental status (West Haven Criteria) • Number Connection Test-A • Venous blood ammonia
	Overt	Unclear	
Merz 1994b[2]	Minimal	Minimal	• Unknown
	Overt	Unclear	
Mittal 2011	Minimal	Minimal	• Mental status (West Haven criteria) • Number Connection Tests-A and -B • Figure Connection Tests-A and -B • Arterial blood ammonia
Ndraha 2011	Minimal	Minimal	• Mental status (West Haven Criteria) • Plasma ammonia • Critical Flicker Frequency
Nimanong 2010[2]	Acute: Grade II or III	Episodic	• Mental status (West Haven Criteria) • Asterixis • Number Connection Test • Electroencephalogram • Plasma ammonia • Portal Systemic Encephalopathy Sum & Index[3]
Oruc 2010[2]	Acute	Episodic	• Mental status (West Haven criteria) • Fasting plasma ammonia • Critical flicker frequency
Poo 2006	Chronic persistent: Grade I or II	Persistent	• Mental status (West Haven Criteria) • Number Connection Test-A • Asterixis • Venous blood ammonia • Portal Systemic Encephalopathy Sum & Index[3]

Table 1. Definitions and assessment of neuropsychiatric status in the include studies with corresponding recommended definitions in the EASL/AASLD guidelines *(Continued)*

Puri 2010[2]	Minimal	Minimal	• Number Connection Test • Digit Symbol Test • Block Design Test • Blood ammonia • Cognitive Evoked Potential-P300 • Critical Flicker Frequency.
Schmid 2010[2]	Minimal Chronic: Grade I or II	Minimal	• Mental status (West Haven Criteria) • Number Connection Tests-A and -B • Digit Symbol Test • Line Tracing Test • Serial Dotting Test • Arterial blood ammonia • Portal Systemic Encephalopathy Sum & Index[3] • Critical Flicker Frequency
	Chronic: Grade I or II	Persistent	
Sharma 2014	Minimal	Minimal	• Clinical Hepatic Encephalopathy Staging Scale (CHESS) • Number Connection Test-A • Figure Connection Test-A • Digital Symbol Test • Critical Flicker Frequency
Sidhu 2018	Acute: Grade II to IV	Episodic	• Mental status (modified West Haven Criteria) • Venous blood ammonia
Stauch 1998	Minimal	Minimal	• Mental status (West Haven Criteria) • Number Connection Test-A • Fasting and postprandial venous blood ammonia • Portal Systemic Encephalopathy Sum & Index[3]
	Chronic: Grade I or II	Persistent	
Taylor-Robinson 2017[1]	Unimpaired	Unimpaired	• Number Connection Test-A • Serial Dotting Test • Line Tracing Test • Digit Symbol Test • Cogstate test battery • Stroop test • Wechsler test of adult reading
	Minimal	Minimal	
Varakanahalli 2017[4]	Unimpaired	Unimpaired	• Mental status • Number Connection Test • Figure Connection Test • Digit Symbol Test • Serial Dotting Test • Line Tracing Tes • Arterial ammonia • Critical Flicker Frequency
Zhou 2013	Acute	Episodic	• Hasegawa's dementia scale • Mini Mental State Examination (MMSE) • Portal Systemic Encephalopathy Sum & Index[3] • Cerebral magnetic resonance Imaging

AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver.
[1]Trials of L-ornithine L-aspartate used for primary prevention.
[2]Not included in the analysis of hepatic encephalopathy versus placebo or non-intervention.
[3]Portal-systemic encephalopathy (PSE) sum and index (Conn 1977), which is calculated using 5 variables: mental status, presence and severity of asterixis; Number Connection Test-A time, blood ammonia concentration, and the electroencephalogram mean dominant frequency. Each variable is assigned a score of 0 (no abnormality) to 4 (severe abnormality); mental status is weighted by a factor of three; PSE index calculated as the ratio of the points scored and the maximum possible score of 28.
[4]Trial of L-ornithine L-aspartate used for secondary prevention.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	December 2017	(ornit* and aspart*) and hepatic encephalopath*
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2017, Issue 11	#1 ornit* in All Text #2 MeSH descriptor Ornithine explode all trees #3 aspart* in All Text #4 MeSH descriptor Aspartic Acid explode all trees #5 (#1 or #2) and (#3 or #4) #6 cirrhosis in All Text #7 Encephalopath* in All Text #8 MeSH descriptor Hepatic Encephalopathy explode all trees #9 #6 or #7 or #8 #10 #5 and #9
MEDLINE Ovid	1946 to December 2017	#1 Randomized controlled trial pt. #2 Controlled clinical trial.pt. #3 exp Randomized controlled trial/ #4 exp Random allocation/ #5 exp Double-blind method/ #6 exp Single-blind method/ #7 clinical trial.pt. #8 exp clinical trial/ #9 (clin$ adj25 trial$).ti,ab. #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #11 singl$ or doubl$ or tripl$ or trebl$).ti,ab. #12 (blind$ or mask$).ti,ab. #13 #11 and #12 #14 exp Placebos/ #15 placebo$.ti,ab. #16 random$.ti,ab. #17 #14 or #15 or #16 #18 #10 or #13 or #17 #19 animals/ not humans/ #20 #18 not #19 #21 exp Ornithine/ #22 exp Aspartic Acid/ #23 #21 and #22 #24 (ornit$ and aspart$).ti,ab. #25 #23 or #24 #26 exp Hepatic Encephalopathy/

(Continued)

		#27 Encephalopathy.ti,ab. #28 cirrhosis.ti,ab. #29 #26 or #27 or #28 #30 #20 and #25 and #29
Embase Ovid	1974 to December 2017	#1 Controlled study/ #2 Randomized Controlled trial/ #3 double blind procedure/ #4 single blind procedure/ #5 crossover procedure/ #6 drug comparison/ #7 placebo/ #8 random*.ti, ab. #9 crossover.ti,ab. #10 cross-over.ti, ab. #11 placebo*.ti,ab. #12 ((doubl* or singl* or tripl* or trebl*) AND (blind* or mask*)).ti, ab. #13 (comparative AND trial*).ti,ab. #14 (clinical AND trial*).ti,ab. #15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 #16 nonhuman/ #17 animal/ not (human/ and animal/) #18 #16 or #17 #19 #15 not #18 #20 'aspartic acid'/ #21 'ornithine'/ #22 #20 and #21 #23 ornit*.ti, ab. #24 aspart*.ti, ab. #25 #23 and #24 #26 #22 or #25 #27 'hepatic encephalopathy'/ #28 encephalopath*.ti, ab. #29 #27 or #28 #30 #19 and #26 and #29
Science Citation Index Expanded (Web of Science)	1900 to December 2017	#1 TS=(ornit* and aspart*) #2 TS=(hepatic encephalopath*) #3 #1 and #2 #4 TS=(random* OR blind* OR placebo* OR meta-analys* OR systematic review*) #5 #3 and #4
LILACS (Bireme)	1982 to December 2017	((ornithin$ AND aspart$) or (LOLA or aksohep or analiv or biohep or hepa-merz or hepalon or hepawin or livogard or livotop or longliv or lornit or orniliv or trisoliv or enervin or hepalex or hepatone or levijon or merzepa or ornamin or ornivit)) [Words] and (liver cirrho$ or hepatic encephalopath$) [Words]

WHAT'S NEW

Date	Event	Description
17 June 2019	Amended	In one paragraph in the Resullts section, the dose of L-ornithine L-aspartate is wrongly designated in mg rather than g.

CONTRIBUTIONS OF AUTHORS

ETG, CSS, LLG, and MYM extracted data.
ETG and LLG analysed data.
ETG, LLG, and MYM undertook the writing of the draft for the present version of the review.

All review authors participated in the interpretation and critical revision of the result of the analyses All review authors approved the final version.

DECLARATIONS OF INTEREST

ETG: nothing to declare.
CSS: nothing to declare.
SS: nothing to declare.
HV: nothing to declare.
LLG: Abbvie, Merck, Norgine (investigator in trials), Novo Nordisk (travel expenses), Norgine (teaching), and Alexion (funding for research).
MYM: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- No funding, Other.

External sources

- No funding, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Based on the available data, we excluded the secondary outcome measure of liver-related mortality because this was included in the analysis of serious adverse events. In addition, we originally planned to evaluate several exploratory outcomes (number connection test, Portal Systemic Encephalopathy Index, and electroencephalography). Based on peer review comment, which we had also received in relation to another review evaluating interventions for hepatic encephalopathy, we chose to omit these data.

INDEX TERMS

Medical Subject Headings (MeSH)

Dipeptides [adverse effects] [*therapeutic use]; Hepatic Encephalopathy [*drug therapy] [mortality] [*prevention & control]; Liver Cirrhosis [*complications]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans